Mechanism and Origins of Stereoselectivity of the Aldol-Tishchenko Reaction of Sulfimines

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ABSTRACT: Density functional theory computations have elucidated the mechanism and origins of stereoselectivity in McGlacken’s aldol-Tishchenko reaction for the diastereoselective synthesis of 1,3-amino alcohols using Ellman’s t-butylsulfimines as chiral auxiliaries. Variations of stereochemical outcome are dependent on the nature of the ketone starting materials used, and the aspects leading to these differences have been rationalized. The intramolecular hydride transfer step is the rate- and stereochemistry-determining step, and all prior steps are reversible.

The aldol-Tishchenko reaction is a powerful means for construction of 1,3-diols through the stereoselective reaction of an enolate with 2 equiv of aldehyde. While this type of reaction has been known for over 100 years, it was only in the 1990s that a mechanistic understanding of the transformation was developed. In subsequent years, the use of chiral ligands, such as BINOLs and cinchona alkaloids, made asymmetric variants possible.

In 2015, McGlacken and co-workers reported the stereoselective synthesis of 1,3-amino alcohols through an aldol-Tishchenko process (Scheme 1). Diastereoselectivity was imparted through the use of t-butylsulfimines, the Ellman auxiliaries. After an initial aldol reaction (1 to 2), the resulting alkoxide reacts with another equivalent of the aldehyde (2 to 3), followed by an intramolecular hydride transfer, to produce the sulfimamide (4). The ester and the chiral auxiliary can then be cleaved to produce a 1,3-amino alcohol.

A variety of substrate classes could be used to form the aldol-Tishchenko product in high yield and diastereoselectivity, including sulfimines derived from propiophenone, acetophenone, and dimethylcyclopentanone (Scheme 2). Surprisingly, the diastereochemical outcome of the reactions was different depending on the starting material: whereas all substrates produced the 1,3-anti product, the relative stereochemistry of the sulfimine t-Bu group and the amine was anti in the case of the propiophenone-derived substrates, and syn in the case of the acetophenone- and dimethylcyclopentanone-derived sulfimines.

These substrates differ both by the identity of the aldehyde that reacts with the sulfimine, as well as by the substitution of the starting material. Experimentally, the use of pivaldehyde was not successful with the propiophenone-derived starting materials, and benzaldehyde was not successful with acetophenone-derived substrates, and thus these factors could not be easily disentangled through experimental studies.

We now report computational studies of the mechanism to determine what factors control the stereoselectivity of the

Scheme 1. Synthesis of 1,3-Diols via the Aldol-Tishchenko Reaction
reaction. In particular, we sought to determine why (1) the 1,3-anti product is favored in all cases and (2) the stereochemistry is different for different types of substrates. Furthermore, the stereochemical orientation of products from dimethylcyclopentanone-derived substrates has been unequivocally identified using crystallography. Despite the fact that deprotonation occurs at a methylene rather than a methyl group, the stereochemistry matches that of the acetophenone-derived substrates, not the propiophenone-derived ones. Again, this has been rationalized using extensive calculation.

DFT calculations were performed with Gaussian 16 to analyze what factors control the stereoselectivity for different substrates. For each structure, an extensive conformer search was performed with CREST to locate the lowest-energy conformer of reactants and transition states. Geometry optimizations were performed with the B3LYP functional, augmented with Grimme’s D3 empirical dispersion term, and the 6-31G(d) basis set. Frequency calculations confirmed the optimized structures as minima (zero imaginary frequencies) or transition state structures (one imaginary frequency) on the potential energy surface. Intrinsic reaction coordinate (IRC) calculations were performed in order to connect the transition states to the reactants and the products. Single point energies were calculated using M06-2X-D3/6-311+G(d,p), and a quasi-harmonic correction was applied using the GoodVibes program.

Experimental studies of the aldol-Tishchenko reaction by McGlacken and co-workers have shown that the steps leading to the final intramolecular reduction step are reversible, and that the reduction step determines the stereochemical outcome of the reaction. Thus, our calculations were focused on the reduction step in order to determine why a change in stereochemistry was observed between the propiophenone substrates compared to the acetophenone and dimethylcyclopentanone substrates, as well as what factors control selectivity.

We first examined the propiophenone-derived sulfinimine, which formed product 6’ in 87% yield and 84:16 dr (Figure 1). In this case, one major diastereomer was observed out of a possible eight. The absolute stereochemistry of the major diastereomer was confirmed by X-ray crystallographic analysis as the (S,R,R,R)-diastereomer. The absolute configuration of the minor diastereomer has not been determined.

Various solvation models were evaluated for computational modeling of the intramolecular hydride step of the reaction sequence. Inclusion of explicit solvents has been shown to be important for calculations of other Li complexes. The starting material for hydride transfer wherein Li is coordinated to two THF molecules was lowest in energy, compared to the mono-solvated (ΔΔG = 3.7 kcal/mol) and unsolvated (ΔΔG = 10.9 kcal/mol) systems. However, the activation barriers (ΔGTS) for the reduction step using the unsolvated, mono-solvated, and di-solvated complexes were similar: 14.6, 14.0, and 14.5 kcal/mol, respectively. In the mono-solvated complex, the lithium cation is tetra-coordinated and bound to one THF molecule, two O-atoms, and the N-atom. In the di-solvated complex, the lithium cation is tetra-coordinated and bound to one THF molecule, two O-atoms, and the N-atom. In the di-solvated complex, the lithium cation is tetra-coordinated and bound to one THF molecule, two O-atoms, and the N-atom. In the di-solvated complex, the lithium cation is tetra-coordinated and bound to one THF molecule, two O-atoms, and the N-atom.

Figure 1. (a) Aldol-Tishchenko reaction of propiophenone-derived sulfinimine. (b) Free energies of starting material structures with various explicit solvation models. (c) Transition states for intramolecular hydride transfer reactions with various explicit solvation models.
case, the lithium cation loses N-coordination but remains tetra-coordinated, which lowers the energy of the complex. The disolvated lithium complex was found to be the lowest in energy and was thus used for comparison of the factors affecting the hydride transition states for various substrates.

The formation of eight different diastereomers is possible in the aldol-Tishchenko reaction of propiophenone-derived starting material 5. The transition state barriers for all eight diastereomers were calculated, and the three lowest-energy transition states are shown in Figure 2. Consistent with experimental results, formation of product (S,R,R,R)-6 proceeds with the lowest-energy transition state barrier (14.5 kcal/mol). The difference between the two lowest transition state barriers (0.6 kcal/mol) is consistent with the experimental dr of 86:14 and would correspond to a dr of 84:16 at −78 °C and 78:22 at −20 °C.

The reaction leading to major product (S,R,R,R)-6 proceeds via a six-membered chair transition state (TS-2a) in which each of the substituents is placed in an equatorial orientation around the six-membered ring (Figure 2). In the lowest-energy transition state, the t-Bu group is optimally oriented away from the ring in order to avoid unfavorable steric interactions. This dictates the relationship between the S and C-N stereocenters. The relative relationship between the stereocenters at C1 and C3 is trans in the transition state for formation of the major product because this allows for the Ph group to be equatorial in the chairlike transition state. The transition states toward hydride transfer were also calculated for the second and third major contributors to the diastereomeric transition states. The second-lowest-energy transition state (TS-2b, ΔΔG° = 0.6 kcal/mol) leads to the stereochemistry analogous to that observed in the acetophenone-derived substrates. In this transition state structure, an unfavorable steric interaction exists between the equatorial methyl group and the t-Bu group of the sulfimine, with a distance of 2.34 Å between these two groups. The penalty for placing the methyl substituent in an axial orientation is 0.9 kcal/mol, leading to TS-2c.

In the cases of the propiophenone substrate, the transition states containing the Z-isomer of the imine led to the major diastereomers of product. Computational results revealed that transition states containing the E-isomer were significantly higher in energy. For example, the transition state leading to the experimentally confirmed major diastereomer (S,R,R,R)-6 using the E-isomer was found to be higher in energy by 6.4 kcal/mol in comparison to the Z-isomer (Figure 3). This may be due to the steric interactions between the sulfimine t-Bu group and the C2 methyl group, which are only 2.28 Å apart. In addition, calculations predict that hydride transfer reactions in which only the E-isomer of the sulfimine is accessible would lead predominantly to formation of a different diastereomer (S,S,S,S), which is inconsistent with experimental results. We thus conclude that the transition state for intramolecular hydride transfer in the propiophenone-derived series proceeds with the Z-isomer of the sulfimine.

Experimentally, acetophenone substrate 7 formed product 8 in 70% yield and 91:9 dr (Figure 4). The absolute stereochemistry of the major diastereomer was assigned as (S,S,S) using X-ray crystallographic data. A reversal of absolute stereochemistry was observed for the acetophenone series (at C1 and C3) in comparison to the propiophenone substrate. In this system, there is a potential for the formation of four diastereomers, but only two diastereomers were observed under the reaction conditions. The absolute stereochemistry of the minor diastereomer was tentatively assigned (S,R,R) by comparison of all four diastereomerically pure samples, using 1H NMR and 13C NMR data.

A similar DFT analysis was performed for the acetophenone derived reaction (Figure 4). In this case, transition state TS-3b leading to formation of minor product (S,R,R)-8 is higher in energy than transition state TS-3a-E, which leads to formation of the major product, by 2.4 kcal/mol. This calculated difference overestimates the diastereoselectivity of the reaction (91:9 dr), as it would correspond to a selectivity of over 99%,
but is consistent with the correct stereochemical outcome. As depicted in Figure 4, unfavorable steric interactions between the large \( t \)-Bu groups appended to the six-membered ring and the THF molecules on Li in the minor transition state (TS-3b) lead to preference for formation of the major diastereomer through TS-3a-E, where these interactions are not present. In TS-3b, the distance between the \( t \)-Bu group at C3 and the THF molecule is 2.27 Å. The \( t \)-Bu group of the sulfimine is also positioned closer to the Ph group attached to the imine. In the case of the acetoephone-derived substrates, the \( E \)-isomer is strongly preferred to the \( Z \)-isomer (by 12.6 kcal/mol) in order to avoid unfavorable steric interactions between the \( t \)-Bu group of the sulfimine and the \( t \)-Bu group of the ester.

In order to test our hypothesis that the additional methyl substituent on the propiophenone substrate plays the main role in reversing the selectivity, and not the \( t \)-Bu vs Ph substituents on the aldehyde that participates in the aldol-Tishchenko reaction, we performed calculations using substrates lacking this methyl group (Figure 5). Indeed, when the methyl group was removed, the lowest-energy product was the one in which the relative stereochemistry of the sulfimine \( t \)-Bu group and the amine was syn, as in the acetoephone-derived substrates, thus leading to a reversal of selectivity. The transition state barrier toward formation of the syn product was 2.1 kcal/mol lower than that toward formation of the anti product, which is close to the difference in transition state barriers for the two products formed from the acetoephone-derived substrates (TS-3a-E vs TS-3b, \( \Delta \Delta G^\ddagger = 2.4 \) kcal/mol). Here, similar factors influence selectivity as in the acetophenone case (Figure 4). This suggests that substitution at C2 leads to the reversal of selectivity.

Analysis of these substrates computationally also allows for a direct comparison of the effects of the substituents derived from the aldehyde component (Ph in the reaction of 5 to 6 and \( t \)-Bu in the reaction of 7 to 8). These model substrates in effect replace the Ph substituents in TS-3 with \( t \)-Bu substituents. The stereochemical outcome is the same in the case of both \( t \)-Bu and Ph, with similar \( \Delta \Delta G^\ddagger \) for both (2.1 vs 2.4 kcal/mol). These results suggest that the steric and electronic differences between the \( t \)-Bu and Ph groups do not have a significant effect on stereoselectivity.

A similar analysis was performed with dimethylcyclopentyl substrate 9 (Figure 6). For this substrate, very good yields and excellent stereoselectivities were observed experimentally using
pivaldehyde and benzaldehyde as aldol acceptors. The reaction of dimethylcyclopentyl sulfinimine 9 and benzaldehyde was chosen as our model. To investigate the origin of stereoselectivity for this reaction, eight transition states were located, three of which are shown in Figure 6. McGlacken and co-workers had tentatively assigned the stereochemistry by analogy to the propiophenone substrate, the (S,R,R,R)-6', because a crystal structure could initially not be obtained. This stereochemistry would be obtained from a fully equatorial arrangement of the substituents during the six-membered ring transition state.

A high-energy transition state barrier was obtained for the product with stereochemistry analogous to that of the propiophenone-derived product (TS-5c). This transition state was 20.3 kcal/mol higher in energy than the lowest-energy transition state TS-5a and led to product (S,R,R,R)-10. One of the lowest energy transition states, TS-5b is 2.7 kcal/mol higher in energy than the lowest-energy transition state, TS-5a. This energy difference corresponds to a dr of 99.9:0.1 at −78 °C and 99.5:0.5 at −20 °C and is thus consistent with the experimental dr of >98:2. Structure TS-5b differs from TS-5c by the stereochemistry of C2, which shows that the equatorial orientation of the cyclopentyl ring is highly disfavored.

The stereoselectivity of this reaction is in line with that of the acetophenon substrate, and similar steric interactions disfavor the minor diastereomer. Although an extra substituent is present at the C2 position, as in the propiophenone-derived substrates, this substituent causes lesser steric strain when it is in the axial position. Conversely, the equatorial configuration of the cyclopentyl ring in TS-5c leads to highly unfavorable steric interactions between the t-Bu group of the sulfimine and the t-Bu group on the cyclopentyl ring.

Further analysis of the NMR spectra suggests that the stereochemistry between positions C2 and C3 is syn, as evidenced by the low coupling constant between the protons at these positions. The high coupling constant between the protons at C1 and C2 suggests an anti relationship. Compound (S,S,R,S)-10, which is formed through TS-5a, satisfies both of these criteria.

The computationally predicted orientation of the dimethylcyclopentanone-derived products matched that of acetophenone rather than propiophenone-derived compounds, despite the fact that the nature of the deprotonation site is methylene rather than methyl. This somewhat surprising result merited a renewed attempt to crystallize some of the aldol-Tishchenko products from this series. Indeed, we obtained crystal structures of the products of the reactions of dimethylcyclopentyl imine 9 with 4-fluorobenzaldehyde and 4-methylbenzaldehyde. These crystal structures matched the computationally predicted stereochemistry, as in compound (S,S,R,S)-10. Similarly, the use of other benzaldehyde derivatives led to products with high diastereoselectivity (Table 1).

The factors governing the selectivities of the aldol-Tishchenko reactions were determined by DFT calculations. Experimental investigations revealed an initial nonselective aldol step, and our computational studies focused on the irreversible and selectivity-determining intramolecular hydride transfer. These studies showed that the relationship between the C1 and C3 stereocenters is preferentially anti because this allows for the Ph or t-Bu group on C3 to be equatorial in the chairlike transition state. The cis/trans relationship between the S-t-Bu of the sulfimine and C1−N is correlated to whether the transition state proceeds via the Z- or E-isomer of the sulfimine: the anti product is formed through the Z-isomer, and the syn product is formed through the E-isomer. In the propiophenone-derived series, unfavorable steric interactions between the equatorial methyl group at C2 with the t-Bu group of the sulfimine prevent the stereochemical outcome analogous to that observed with the acetophenone-derived substrates, and thus lead to a reversal of stereoselectivity.

Our study explains the origin of stereoselectivity for the aldol-Tishchenko reaction of sulfynilimines and provides a guide to the selectivities expected for related reactions. In addition, we demonstrate the power of the interplay between computational and synthetic chemistry for predictions of stereochemical outcome and structure determination.

**EXPERIMENTAL SECTION**

**General Information.** Solvents were dried and stored over flame-dried 4 Å molecular sieves (10–15% w/v) in a Young’s flask. The concentration of n-BuLi in hexanes was determined by titration with diphenylacetic acid. All aldehydes were freshly distilled prior to use and stored under an inert atmosphere. All other reagents were purchased from Sigma-Aldrich, Fluorochem, Alfa Aesar, and Acros unless otherwise noted. All nonaqueous reactions were carried out under an oxygen-free nitrogen atmosphere using oven-dried glassware.

Wet flash column chromatography was carried out using Kieselgel silica gel 60, 0.040–0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF254). Visualization was achieved by UV and potassium permanganate staining. Melting points were measured on a Thomas Hoover Capillary Melting Point apparatus. Infrared (IR) spectra were recorded on a PerkinElmer FT-IR Paragon 1000 spectrophotometer.

NMR spectra were run in CDCl3 using TMS as the internal standard at 25 °C. 1H NMR (600 MHz) spectra, 1H NMR (400 MHz) spectra, and 1H NMR (300 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 400, and Bruker Avance 300 NMR spectrometers, respectively. 13C (150.9 MHz) spectra, 13C (100.6 MHz) spectra, and 13C (75.5 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 400, and Bruker Avance 300 NMR spectrometers, respectively, in proton decoupled mode. All spectra were recorded at University College Cork. Chemical shifts δH and δC are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (J) are expressed in hertz (Hz). Splitting patterns in 1H NMR spectra are designated as s.
(singlet), br s (broad singlet), d (doublet), dd (doublet of doublets), dt (doublet of triplets), t (triplet), q (quartet), quin (quinet), sext (sextet), sept (septet), and m (multiplet). For 13C NMR spectra, the number of attached protons for each signal was determined using the DEPT pulse sequence run in the DEPT-90 and DEPT-135 modes. COSY, HSQC, and HMBC experiments were performed to aid the NMR assignment of novel chemical structures.

Optical rotations were recorded on a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature device, operating at T = 100 K. The structure was solved with the ShelXT (Sheldrick, 2015) structure solution program using the Intrinsic Phasing solution method and by using Olex2 as the graphical interface. The model was refined with version 2016/6 of ShelXL (Sheldrick, 2015) using Least Squares minimization. Most hydrogen atom positions were calculated geometrically and refined using the riding model, but some hydrogen atoms were re-allowed freely. The model was re-phased using Olex2 as the graphical interface. The model was re-phased, and some hydrogen atoms were re-allowed freely.

1H NMR spectra, 13C NMR spectra, and LRMS and IR analyses were recorded for all previously prepared compounds. For novel compounds, in addition to the previously mentioned analysis, HRMS was also obtained.

In most cases, it was possible to separate the diastereomers; however, the yield reflects the mixture of diastereomers. The major diastereomer was fully characterized in all cases. Diastereoselectivity was determined by analysis of the 1H NMR spectrum of the crude reaction mixture.

Synthesis of Starting Materials. General Procedure for the Synthesis of (S)- tert-Butyl Sulfinate. To a solution of titanium(IV) isopropoxide (0.215 g, 1 mmol) and 4-fluorobenzaldehyde (0.32 mL, 3 mmol) as a white solid (0.312 g, 61% (mixture of diastereomers)). Major diastereomer: Mp 157−159 °C. [α]25 D = −19.4, 8.0, 1.6 Hz), 2.99, 2.86 (2H, m), 3.28 (1H, dt, J = 9.8 Hz), 2.30, 2.43 (2H, s), 3.20 (1H, m), 2.04−1.94 (1H, m), 1.73−1.53 (3H, m), 1.27 (9H, s), 1.17, 0.91 (2 H, 3H, s) ppm. 13C NMR(1H) (77.95 MHz, CDCl3) δ 166.5 (d, JCF = 254.8 ppm), 164.5, 162.5 (d, JCF = 246.5 ppm), 136.2 (d, JCF = 3.3 Hz), 131.2 (d, JCF = 9.3 Hz), 127.9 (d, JCF = 8.2 Hz), 126.3 (d, JCF = 3.2 Hz), 115.8 (d, JCF = 22.0 Hz), 115.4 (d, JCF = 21.4 Hz), 74.2, 69.0, 56.3, 51.7, 40.6, 36.6, 27.3, 22.9, 20.2 ppm. HRMS (ESI) m/z calcd for C12H13FNO5 [M + H]+: 446.5, found 446.256.

(S)-(1R,2S)-2-(((S)-tert-Butylsulfinyl)amino)-3,3-dimethylcyclopentyl)4-fluor phenyl)methyl 4-Fluorobenzoate. 12. Compound 12 was prepared using sulfinilimine (0.215 g, 1 mmol) and 4-fluorobenzaldehyde (0.215 g, 1 mmol) as a white solid (0.278 g, 60% (mixture of diastereomers)). Major diastereomer: Mp 157−159 °C. [α]25 D = −19.4, 8.0, 1.6 Hz), 2.99, 2.86 (2H, m), 3.28 (1H, dt, J = 9.8 Hz), 2.30, 2.43 (2H, s), 3.20 (1H, m), 2.04−1.94 (1H, m), 1.73−1.53 (3H, m), 1.27 (9H, s), 1.17, 0.91 (2 H, 3H, s) ppm. 13C NMR(1H) (77.95 MHz, CDCl3) δ 166.5 (d, JCF = 254.8 ppm), 164.5, 162.5 (d, JCF = 246.5 ppm), 136.2 (d, JCF = 3.3 Hz), 131.2 (d, JCF = 9.3 Hz), 127.9 (d, JCF = 8.2 Hz), 126.3 (d, JCF = 3.2 Hz), 115.8 (d, JCF = 22.0 Hz), 115.4 (d, JCF = 21.4 Hz), 74.2, 69.0, 56.3, 51.7, 40.6, 36.6, 27.3, 22.9, 20.2 ppm. HRMS (ESI) m/z calcd for C12H13FNO5 [M + H]+: 446.5, found 446.256.

(S)-(1R,2S)-2-(((S)-tert-Butylsulfinyl)amino)-3,3-dimethylcyclopentyl)(p-tolyl)methyl 4-Methylbenzoate. 13. Compound 13 was prepared using sulfinilimine (0.215 g, 1 mmol) and 4-methylbenzaldehyde (0.215 g, 1 mmol) as a white solid (0.312 g, 61% (mixture of diastereomers)). Major diastereomer: Mp 157−159 °C. [α]25 D = −19.4, 8.0, 1.6 Hz), 2.99, 2.86 (2H, m), 3.28 (1H, dt, J = 9.8 Hz), 2.30, 2.43 (2H, s), 3.20 (1H, m), 2.04−1.94 (1H, m), 1.73−1.53 (3H, m), 1.27 (9H, s), 1.17, 0.91 (2 H, 3H, s) ppm. 13C NMR(1H) (77.95 MHz, CDCl3) δ 166.5, 143.8, 137.8, 137.1, 129.6, 129.2, 127.6, 125.5, 74.3, 69.0, 56.3, 51.9, 40.6, 36.8, 27.2, 22.9, 21.9, 21.1, 21.7, 20.2 ppm. HRMS (ESI) m/z calcd for C12H14FNO6S [M + H]+: 456.2567, found 456.2565.

(S)-(1R,2S)-2-(((S)-tert-Butylsulfinyl)amino)-3,3-dimethylcyclopentyl)(4-isopropylphenyl)methyl 4-Isopropylbenzoate. 14. Compound 14 was prepared using sulfinilimine (0.215 g, 1 mmol) and 4-isopropylbenzaldehyde (0.45 mL, 3 mmol). The crude compound (91.9 g) was purified using column chromatography on silica gel (3:1, hexane:EtOAc) to give the title compound 14 as a white solid (0.215 g, 61% (mixture of diastereomers)). Major diastereomer: Mp 157−159 °C. [α]25 D = −19.4, 8.0, 1.6 Hz), 2.99, 2.86 (2H, m), 3.28 (1H, dt, J = 9.8 Hz), 2.30, 2.43 (2H, s), 3.20 (1H, m), 2.04−1.94 (1H, m), 1.73−1.53 (3H, m), 1.27 (9H, s), 1.17, 0.91 (2 H, 3H, s) ppm. 13C NMR(1H) (77.95 MHz, CDCl3) δ 165.6, 154.6, 148.0, 138.0, 129.8, 128.0, 126.7, 126.5, 125.6, 74.3, 73.1, 36.8, 27.0, 22.8, 21.9, 21.1, 21.7, 20.2 ppm. HRMS (ESI) m/z calcd for C21H18FNO6S [M + H]+: 456.2567, found 456.2565.
The crude compound (>99:1 dr) was purified using column chromatography on silica gel (4:1, hexane:EtOAc) to give the title diastereomers. Major diastereomer: 

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02862.

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**Notes**

The authors declare no competing financial interest.

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**REFERENCES**

(1) Brauchiar, M.; Kohn, L. Über Condensationsprodukte der Aldehyde. Monatsh. Chem. 1899, 19, 16.

(2) (a) Burkhardt, E. R.; Bergman, R. G.; Heathcock, C. H. Synthesis and reactions of nickel and palladium carbon-bound enolate complexes. Organometallics 1990, 9, 30. (b) Evans, D. A.; Hoveyda, A. H. Samarium-catalyzed intramolecular Tishchenko reduction of β-hydroxy ketones. A stereoselective approach to the synthesis of differentiated anti 1,3-diol monoesters. J. Am. Chem. Soc. 1990, 112, 6447.

(3) (a) Asano, T.; Katoni, S.; Nakajima, M. Stereoselective Synthesis of 2-Fluoro-1,3-Diols via Lithium Binaphtholate-Catalyzed Aldol–Tishchenko Reaction. Org. Lett. 2019, 21, 4192. (b) Gnanadisken, V.; Hachiya, Y.; Ohshima, Y.; Subhaski, M. Direct Catalytic Asymmetric Aldol-Tishchenko Reaction. J. Am. Chem. Soc. 2004, 126, 7782. (c) Ichibakase, T.; Nakajima, M. Direct Enantioselective Aldol–Tishchenko Reaction Catalyzed by Chiral Lithium Diphenylbinaphtholate. Org. Lett. 2011, 13, 1579. (d) Mlynarski, J. Direct Asymmetric Aldol-Tishchenko Reaction. Eur. J. Org. Chem. 2006, 2006, 4779. (e) Mlynarski, J.; Jankowska, J.; Rakiel, B. Direct asymmetric aldol-Tishchenko reaction of aliphatic ketones catalyzed by syn-aminocarboxyl-Yb(iii) complexes. Chem. Commun. 2005, 4854. (f) Mlynarski, J.; Mitura, M. The first example of a catalytic asymmetric aldol–Tishchenko reaction of aldehydes and aliphatic ketones. Tetrahedron Lett. 2004, 45, 7549. (g) Rohr, K.; Herre, R.; Mehrwald, R. Enantioselective Direct Aldol-Tishchenko Reaction: Access to Chiral Stereopentads. Org. Lett. 2005, 7, 4499. (h) Shimoda, Y.; Kubo, T.; Sugira, M.; Kotani, S.; Nakajima, M. Stereoselective Synthesis of Multiple Stereocenters by Using a Double Aldol Reaction. Angew. Chem., Int. Ed. 2013, 52, 3461.

(4) (a) Foley, V. M.; Mcsweeney, C. M.; Eccles, K. S.; Lawrence, S. E.; McGlacken, G. P. Asymmetric Aldol–Tishchenko Reaction of Sulfinimines. Org. Lett. 2015, 17, 5642. (b) Mackey, P.; Cano, R.; Foley, V. M.; McGlacken, G. P. Preparation of anti-1,3-Amino Alkaloid Derivatives Through an Asymmetric Aldol-Tishchenko Reaction of Sulfinimines. Org. Synth. 2017, 94, 259.

(5) (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. Synthesis and Applications of tert-Butanesulfinamide. Chem. Rev. 2010, 110, 3600. (b) Liu, G.; Cogan, D. A.; Owens, T. D.; Tang, T. P.; Ellman, J. A. Synthesis of Enantiomerically Pure N-tert-Butanesulfinyl Imines (tert-Butanesulfinimines) by the Direct Condensation of tert-Butanesulfonamide with Aldehydes and Ketones. J. Org. Chem. 1999, 64, 1278.

(6) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; et al. Gaussian 16/Gaussian, Inc.: Wallingford, CT, 2016.

(7) Pracht, P.; Bohle, F.; Grimm, S. Automated exploration of the low-energy chemical space with fast quantum chemical methods. Phys. Chem. Chem. Phys. 2020, 22, 7169.

(8) (a) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. MP2 energy evaluation by direct methods. Chem. Phys. Lett. 1988, 153, 503.
(b) Becke, A. D. Density-functional thermochemistry. III. The role of exact exchange. *J. Chem. Phys.* 1993, 98, 5648. (c) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B: Condens. Matter Mater. Phys.* 1988, 37, 785. (d) Vosko, S. H.; Wilk, L.; Nusair, M. Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.* 1980, 58, 1200. (e) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.* 1994, 98, 11623.

(9) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A consistent and accurate ab initio parametrization of density functional dispersion correction (DFT-D) for the 94 elements H-Pu. *J. Chem. Phys.* 2010, 132, 154104.

(10) Zhao, Y.; Truhlar, D. G. The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, non-covalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals. *Theor. Chem. Acc.* 2008, 120, 215.

(11) Paton, R. S.; Rodriguez-Guerra, J.; Funes, J. I. *GoodVibes*, ver. 3.0.0; Zenodo: Geneva, Switzerland, 2019. DOI: 10.5281/zenodo.3346166.

(12) (a) Tallmadge, E. H.; Jermaks, J.; Collum, D. B. Structure−Reactivity Relationships in Lithiated Evans Enolates: Influence of Aggregation and Solvation on the Stereochemistry and Mechanism of Aldol Additions. *J. Am. Chem. Soc.* 2016, 138, 345. (b) Houghton, M. J.; Collum, D. B. Lithium Enolates Derived from Weinreb Amides: Insights into Five-Membered Chelate Rings. *J. Org. Chem.* 2016, 81, 11057. (c) Yu, K.; Lu, P.; Jackson, J. J.; Nguyen, T.-A. D.; Alvarado, J.; Stivala, C. E.; et al. Lithium Enolates in the Enantioselective Construction of Tetrasubstituted Carbon Centers with Chiral Lithium Amides as Noncovalent Stereodirecting Auxiliaries. *J. Am. Chem. Soc.* 2017, 139, 527.