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Practical, Asymmetric Route to Sitagliptin and Derivatives: Development and Origin of Diastereoselectivity

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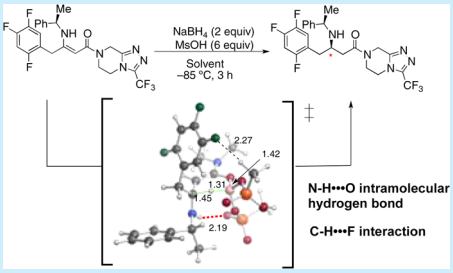
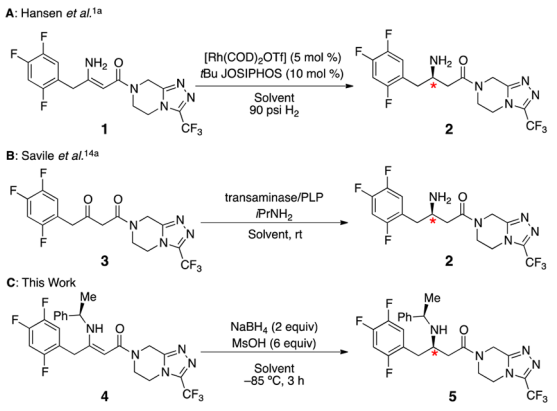
Supporting Information

ABSTRACT: The development of a practical and scalable process for the asymmetric synthesis of sitagliptin is reported. Density functional theory calculations reveal that two noncovalent interactions are responsible for the high diastereoselection. The first is an intramolecular hydrogen bond between the enamide NH and the boryl mesylate S═O, consistent with MsOH being crucial for high selectivity. The second is a novel C−H···F interaction between the aryl C5-fluoride and the methyl of the mesylate ligand.



Stereoselective enamine reduction is one of the most useful methods for the synthesis of enantiomerically pure β-amino carbonyls. In order to attain stereoinduction in these transformations, a sacrificial chiral auxiliary[1−6] or asymmetric metal-catalyzed method is used.[7−9] A noteworthy example is found in the commercial synthesis of sitagliptin (**2**) from reduction of enamine **1** using an expensive rhodium/chiral phosphine combination (Scheme 1, A).[10] The phosphate salt of sitagliptin, discovered by Merck, has been approved by the US FDA for the management of type 2 diabetes mellitus.[11] Sitagliptin inhibits the proteolytic activity of dipeptidyl peptidase-4,[12] an enzyme that breaks down the incretins,[13] which play a key role in glucoregulation by increasing insulin secretion and suppressing glucagon release. More recently, an elegant biocatalytic route to sitagliptin utilizing an engineered transaminase enzyme to covert dicarbonyl **3** to **2** has been developed and commercialized (Scheme 1, B).[14] Although numerous reports on the synthesis of sitaliptin have appeared,[10,17,15] to the best of our knowledge, an inexpensive reagent-based diastereoselective enamine reduction toward sitagliptin remains unprecedented.

Scheme 1. Asymmetric Routes to Sitagliptin



Herein, we report such an alternate approach exploiting the combination of an inexpensive reducing agent ($NaBH_4$/MsOH) and an inexpensive chiral auxiliary (phenethylamine)[16] to accomplish the diastereoselective reduction of β-enamino amide **4** to provide advanced intermediate **5** (Scheme 1, C). This approach also led to the diasteroselective reduction of several analogues of **4**, demonstrating the potential to provide a general route for highly efficient and diastereoselective reductions of enamines. Further, density functional theory was used to assess the role of the chiral auxiliary and substrate on the observed diastereoselectivity. Intramolecular hydrogen bond and CH···F interactions were shown to play key roles in controlling the stereochemical outcome. Subsequent experiments with additional substrates provided support for the computed models.

We initiated our studies by surveying the entire synthetic landscape[17] to **2** to assess the relative merits of all the hitherto known strategies. Although a few chiral auxiliary enamine reduction approaches are reported toward **2**, they utilize costly metal catalysts.[18] Therefore, we attempted to develop a homogeneous reduction system using inexpensive hydride reagents. At the outset of our endeavor, we considered the application of widely used chiral amine (*R*)-(+)-phenyl ethyl amine as an auxiliary. Notably, this material is generated on large scale[19] and is readily available at low cost. Inspection of the key

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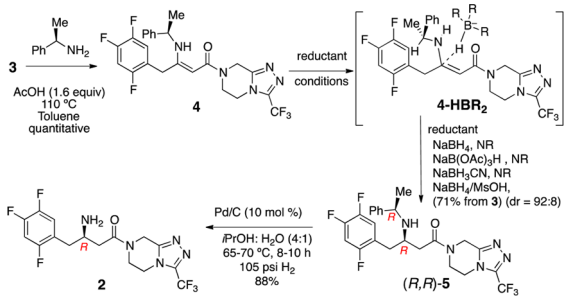
proposed substrate **4** reveals an α,β-unsaturated amide which permits a very different approach relative to metal-catalyzed hydrogenation. It was envisioned that the carbonyl group of the enone would engage in hydrogen bonding with the amino group of the auxiliary giving rise to conformationally well-defined system **4** where the amino group is predominantly sp^2.[20] Consequently, allylic strain[21] would cause the auxiliary to impose a facial bias during external delivery of hydride to the β-site. Specifically, approach to the less-hindered bottom face of the enamide as shown in **4-HBR$_2$** of Scheme 2 would generate the

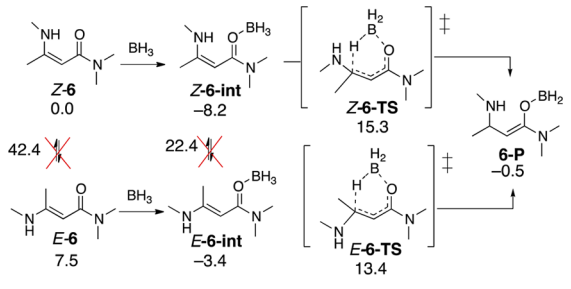
Scheme 2. Synthetic Route to Sitagliptin



targeted stereocenter. Intermediate **4** was synthesized by combining ketoamide **3** and (*R*)-(+)-phenylethylamine in toluene with 1.6 equiv of acetic acid at 110 °C.[22] In this experiment, only the *Z*-isomer was observed in the quantitative conversion to **4** due to the highly stabilizing hydrogen bond described above (see also below).[20]

Having achieved an expedient synthesis of **4**, the next task was to devise a suitable reagent system for reduction. In this context, several borohydride species precedented in the this reduction [$NaBH_4$, $NaB(OAc)_3H$, and $NaBH_3CN$][20] were studied but resulted in no conversion with the β-enamino amide being recovered (Scheme 2). Undeterred, we hypothesized that a Lewis acidic reductant would allow internal hydride delivery, which is not possible with the aforementioned reductants. Addition of 5−6 equiv of MsOH to 2 equiv of $NaBH_4$ generated the requisite $B(MsO)_2H$ in situ.[23] The internal hydride delivery mode provides stereocontrol because interactions from the (*R*)-(+)-phenethylamine would dictate the geometry in the resultant 6-membered transition state (Scheme 3). To our delight, this combination afforded **5** in 71% yield with the target diastereomer predominating (dr 92:8).[24] Furthermore, reaction of *ent*-**4** with the $NaBH_4$/MsOH reagent system afforded *ent*-**5** with same selectivity and efficiency. Hydrogenolysis of the desired diastereomer **4** by means of 10% Pd/C (50% wet) in *i*-PrOH/water at 65−70 °C and 105 psi hydrogen pressure for 10 h readily

Scheme 3. Free Energies of the Model System Reduction[a]



[a]Conditions: 298 K, kcal/mol, B3LYP/6-31G(d) [toluene, CPCM].

afforded sitagliptin (**1**) in 88% yield. The diastereoselectivity in the previous step was retained in this transformation and the Pd catalyst could be recovered and regenerated.[25] Significantly, the previously reported enantioselective catalytic hydrogenation[10] or diastereoselective catalytic hydrogenations[18] all utilized high cost transition metals (Rh, Ru, Pt). As such, this strategy represents a cost competitive approach.

To gain insight into the mechanism and diastereoselectivity, DFT (B3LYP and M062X) calculations[26] were undertaken on the model system using BH_3 as the hydride source (Scheme 3). In accord with experiment, the *Z*-**6** isomer is lower in energy (by ∼8 kcal/mol) than the *E*-**6** enamine isomer due to an intramolecular hydrogen bond. Further, the barrier for interconversion between these two isomers is high (∼42 kcal/mol). Complexation with BH_3 is energetically favored (by ∼3−8 kcal/mol) and significantly reduces the *E*/*Z* interconversion barrier (∼30 kcal/mol); however, this barrier is still high relative to the experimental conditions (−90 °C) and isomerization was therefore not considered. Finally, calculations showed that the hydride transfer process occurs via a 6-membered transition state with overall barrier of 23.5 kcal/mol (from *Z*-**6-int**) and is slightly downhill in energy. Subsequent decomplexation/enol−keto tautomerization delivers the amino amide product.

Next, the origin of the observed diastereoselectivity was investigated by performing extensive conformational modeling of the transition states with the leading to (*R*,*R*)- and (*R*,*S*)-diastereomers using model substrates *Z*-**7-int** (R= phenyl and 2,4,5-$F_3C_6H_2$) and BH_3 as hydride source (see the Supporting Information for structures and energetics). However, these calculations failed to account for the observed diastereoselectivity predicting a low diastereomeric ratio favoring the wrong stereoisomeric product (see Supporting Information).

Experimentally it was shown that the nature of the hydride source had a significant effect on the overall diastereoselectivity (see Scheme 2). As depicted in Figure 1, modeling $B(OMs)_2H$ as hydride source correctly predicts the major diastereomer (*R*,*R*)-**7** albeit only slightly [a Boltzmann distribution of the transition states gives a 35:65 ratio favoring (*R*,*R*)-**7**]. This result highlights the subtle but important interactions the OMs groups have on the diastereoselectivity (see the Supporting Information for other conformers). In addition, these results show a different conformation than that expected based on allylic strain considerations; namely, the methyl group of the α-methylbenzyl is oriented *anti*-periplanar to the enamide C−N bond due to favorable π-stacking interactions between the chiral auxiliary arene and the substrate arene. As a consequence, hydride approach occurs over the α-methylbenzyl hydrogen rather than the phenyl in the lowest energy approaches (Figure 1, *Z*-**7-TS-eq**-*cis* and *Z*-**7-TS-ax**-*trans*); other subtle, nonbonded interactions account for the energetic differences. Notably, modeling with the substrate containing the trifluorinated aryl group (values in parentheses) increased the overall diastereoselectivity in excellent agreement with experiment; the Boltzmann distribution predicts 5:95 ratio in favor of the (*R*,*R*)-diastereomer. The fluorinated aryl ring caused the OMs groups to adopt the conformation shown in *Z*-**7-F-TS-eq**-*cis* (Scheme 4).

Closer inspection of the transition-state structures with the fully fluorinated aryl (Scheme 4) revealed a key intramolecular hydrogen bond between the NH of the amine auxiliary and one of the mesylate S═O groups that stabilizes the *Z*-**7-F-TS-eq**-*cis* transition state structure. Further, this transition state benefits from an intramolecular CH···F interaction "hydrogen bridge"[27,28] between the one of the C−F bonds of the aryl

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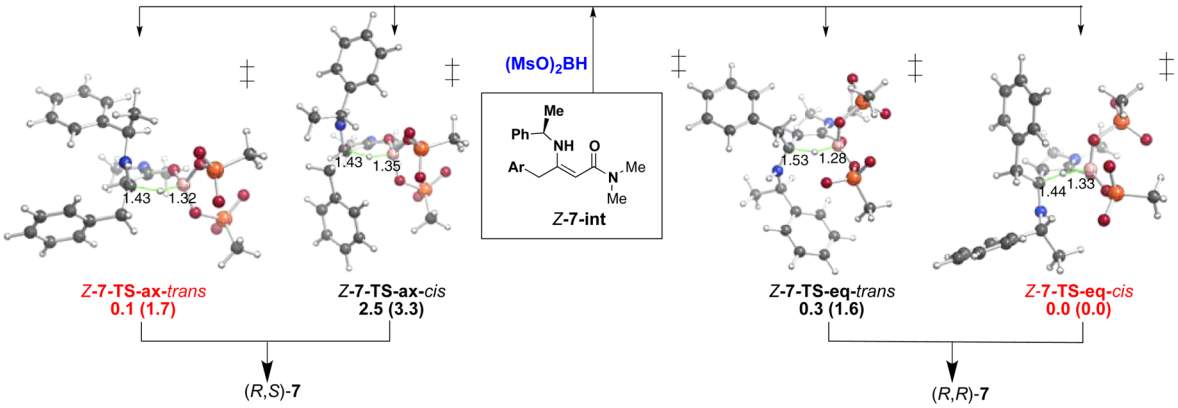
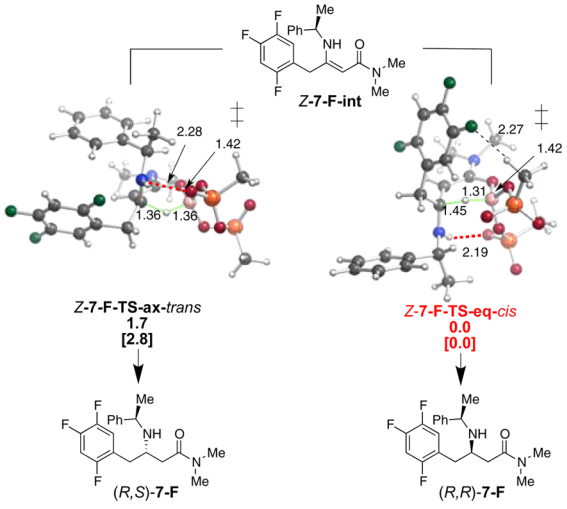


Figure 1. Effect of boron substitution on the diastereoselectivity. Relative enthalpies (kcal/mol) at the B3LYP/6-31G(d) in toluene (CPCM). The first value for each compound is the result for Ar = Ph, the value in parentheses is for Ar = 2,4,5-$F_3C_6H_2$. Structures shown with Ar = Ph.

Scheme 4. . Effect of Aryl Group Substitution on Diastereoselectivity[a]

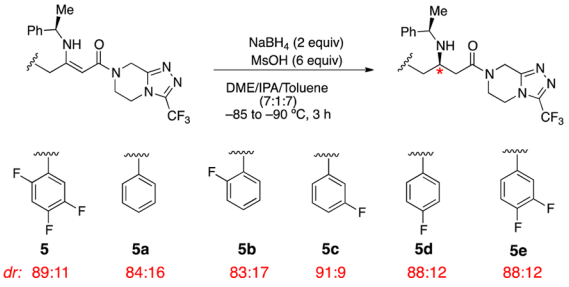


[a]Relative enthalpies, (kcal/mol), B3LYP/6-31G(d) toluene (CPCM); values in brackets and selected distances (Å) are for M062X/6-31G(d) toluene (CPCM) optimized geometries.

group and the CH_3 of the methanesulfonyl. The 2.27 Å intermolecular distance is shorter than the sum of the van der Waals radii which is 2.54 Å.[29] This interaction accounts for the higher selectivity with the fluoro analog. Although CH···F interactions have been observed in crystal structures (CH-F distance 2.26 Å), they are rarely invoked in influencing selectivities and reactivities.[30]

To explore the effects of the fluorines on the diastereoselectivity, several analogues with varying fluorine patterns around the ring were synthesized and subjected to the same reduction (Scheme 5). In agreement with computations, the fluorines do play a role in on the experimentally observerd diasteroselectivity. Overall, the 5-fluoro substituent has the greatest impact on the stereoselectivity, consistent with the calculations. However, the effects of the fluoro groups do not appear additive indicating that additional factors such as their influence on the conformational space are likely to play a role in the diastereoselective reduction (see the Supporting Information). Due to the computational cost and minor changes on diastereoselectivity (within the limits of computational errors) the role of each individual fluorine atom was not explored further.

Scheme 5. Effect of Aryl Group Substitution on Experimental Diastereoselectivity



In comparison to previously reported synthesis of sitagliptin, this strategy offers a very efficient and workable protocol with at least four salient features: (1) facile stereoselective access to a single *Z*-isomer starting material, (2) a protocol that does not require high hydrogen pressures, (3) high conversion, and (4) very good diastereoselectivity (92:08). Such a diastereoselective strategy permits ready separation of the minor diastereomer from the mixure to obtain the major diastereomer in very pure form (>99.9:0.1), thereby increasing the isolated yield and overall efficiency of the procedure. Further, this diastereoselective approach does not require repeated purification to achieve stereochemical enrichment, as is the case in alternative enantioselective approaches. In conclusion, a scalable and economical process has been developed to access advanced sitagliptin intermediate **5** via homogeneous reagent-based reduction with excellent diastereoselectivity. Density functional theory was used to gain insight into the observed mechanism of asymmetric induction. Analysis of the relevant tranisiton states revealed two key noncovalent interactions, an intramolecular hydrogen bond and a novel C–H···F interaction, between the chiral auxiliary and the hydride source that serve as control elements.

■ ASSOCIATED CONTENT

Supporting Information

Complete computational details, complete ref 26 for Gaussian09, experimental procedures, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(26) All calculations were optimized in toluene (CPCM model) at the B3LYP/6-31G(d) [and/or M06-2X/6-31G(d)] level, as implemented in Gaussian09: Frisch, M. J.; et al. *Gaussian 09*, rev performed using GAUSSIAN09, revision A.02; Gaussian, Inc.: Wallington, CT, 2009. Additional details can be found in the Supporting Information.

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