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Theoretical Investigation on Direct Vinylogous Aldol Reaction of Isatin Catalyzed by Chiral-*N*, *N*′-dioxide Sc(III) Complex

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ABSTRACT

The mechanism and *enantio*- as well as diastereo-selectivity of asymmetric direct aldol reaction of isatin with α-angelica lactone catalyzed by chiral *N*, *N*′-dioxide-Sc(OTf)$_3$ were studied at the B3LYP(SMD, THF)/6-31G(d,p) level. The calculations indicated that the reaction occurred along stepwise mechanism, that is, C—C bond formation followed by H-transfer from α-angelica lactone to carbonyl group of isatin. The H-transfer step was predicted to be the rate-determining step(RDS), with the energy barrier of 23.3 ~ 26.2 kcal mol^{-1} for four stereoisomeric products. The *ortho*-isopropyl groups of amide in ligand blocked the reacting site from *re*-face of isatin and induced the *re*-face of α-angelica lactone to approach to the *si*-face of isatin, leading to the predominant product with 3*S*, 2′*S*-configuration. In this asymmetric catalysis, the interaction energy term (ΔE_{int}), especially stabilizing orbital energy (ΔE_{oi}) and electrostatic energy (ΔV_{elstat}), were the main contributors to the enantioselectivity of the reaction, while the activation strain energy (ΔE_{strain}) of α-angelica substrate enhanced the diastereodifferentiation of the two competing pathways, contributing to high diastereomeric ratio (d.r.). The turnover frequency (TOF) along the favorable *si*-face pathway was predicted to be 2.76 × 10^{-21} s^{-1}, with the rate constant of $k(T) = 7.5 \times 10^{-2}$ exp(-108390/RT) dm^3 mol^{-1} s^{-1} over 258.15 K ~ 358.15 K temperature range. These results provided explanation for the good reactivity as well as excellent asymmetric induction of chiral *N*, *N*′-dioxide-Sc(OTf)$_3$ in direct aldol reaction of isatin.

Introduction

Aldol condensation was one of the most important methods for creating a C—C bond in nature [1–3], which provided versatile biologically active and pharmaceutically key building blocks for the synthesis of many compounds. Since the pioneering work by List, Barbas, and co-workers in 2000 [4,5], organocatalyst as a simple chemical mimic for enzymes has received much attention [6,7].

The proline-catalyzed aldol reactions were proved to proceed through an enamine-mediated mechanism [8–11]. The hydrogen bonding between the partial positive hydrogen of the carbon adjacent to the proline nitrogen and the aldehyde substrate stabilized the transition state well, accelerating C—C bond formation [8]. Some amine catalysts (such as cinchona alkaloid and bispidine derivative) also exhibited good catalytic behaviors and chirality-controlling for asymmetric direct aldol reaction [6,7,12–15]. The basic N atom induced the deprotonation of substrates and oriented the carbonyl by hydrogen bonding for high stereoselectivity outcomes [6,12].

In contrast to the remarkable advances made in organocatalysis, the application of organometallic catalysts in direct aldol reaction was limited. The metal-catalyzed aldol reaction usually involved the coordination of carbonyl compounds to metal centre, which increased efficiently their electrophilicity for attack by nucleophiles [16]. Hanessian and co-workers studied the LiBr-catalyzed intramolecular aldol cyclizations towards carbocyclic tertiary *β*-ketols at the ωB97x-D/def2TZVP theoretical level. The calculations indicated that LiBr could engage in a bifunctional coordination of two carbonyl moieties of triketone substrate, forming a spatially pre-organized Li-coordinated reactive 1,5-enolate/carbonyl intermediate for a base-mediated intramolecular aldol cyclization [14]. Theoretical studies on the diastereoselective aldol reaction of 3-chloro-3-methyl-1-aza allylic anions and benzaldehyde revealed that the formation of a highly ordered bimetallic six-membered twist-boat-like transition state with a tetracoordinated metal cyclic structure played an important role for the high *syn* diastereoselectivity reaction [17]. The aldol reactions catalyzed by Zn(II) complexes(for example Zn-BINOL [18,19], Zn-semicrown ethers [20–22], Zn(L-proline)$_2$ [23], Zn-cycle [24]) were assumed to follow the class II aldolases mechanism, forming reactive Zn^{2+}-enolate intermediates. Penhoat et al. demonstrated that direct combination of the chloride salts of the group 12 elements($ZnCl_2$, $CdCl_2$ or $HgCl_2$) and L-

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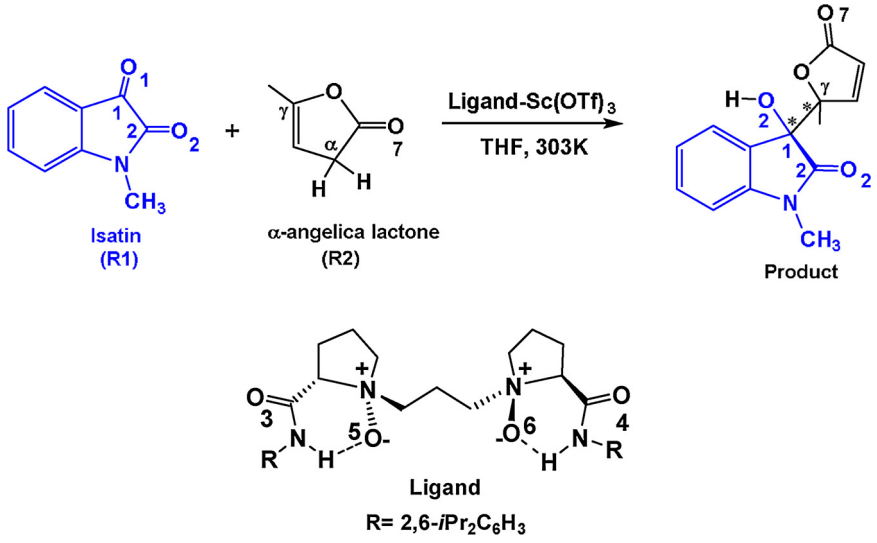
proline could form co-catalysts and promote direct aldol reaction of cyclohexanone with aromatic aldehydes *via* a reactive species analogous to class II aldolases [3,25].

A enamine-metal Lewis acid bifunctional catalytic strategy was also applied in direct asymmetric aldol reaction [26–28]. In the catalysis, the metal coordinated with ligand to form a rigid chiral structure and activated the aldol acceptor as Lewis acid, while the amine reacted with aldol donor to form an enamine intermediate [26]. Mlynarski reported bisprolinamide-zinc complexes-catalyzed direct asymmetric aldol reactions of acetone and cyclohexanone in aqueous media [28]. A transition state model was proposed, in which Zn centre stabilized enamine intermediates by interacting with the N and carbonyl group of a proline unit of chiral ligand, and activated simultaneously the aldehyde by coordination interaction. In the metal-templated bifunctional organocatalysts formed by metal salt ($CuSO_4$ or $ZnCl_2$), pyridine-based prolinamide and thiourea ligand, the role of the metal centre in aldol reaction was assumed to provide the assembly point for the organocatalytic ligand in the aldol reaction [29].

In 2011, Feng's group used chiral *N*, *N*′-dioxide-Sc(OTf)$_3$ as a catalyst for direct asymmetric aldol-type reaction of 3-substituted-2-oxindoles, constructing 3-(α-hydroxy-*β*-carbonyl) oxindoles with vicinalquaternar-tertiary or quaternary–quaternary stereocenters in excellent diastereo- and *enantio*-control. A chiral scandium enolate was assumed to be the reactive species, which interacted with the coordinated phenylglyoxal substrate in bidentate fashion to form intermediate [30]. Recently, they found that this Sc(III)-complex was also efficient in the aldol reaction of isatin substrate with non-activated α-angelica lactone, providing the *δ*-hydroxy butenolides products with congested adjacent tetrasubstituted stereocenters in good diastereoselectivity (> 19/1 d.r.) and excellent enantioselectivities (98% *ee*) [31]. Based on the nonlinear effect results and ESI–MS analysis obtained in experiments, a monomeric catalytic active species was proposed, and the repulsion between and *N*-methyl of isatin and γ-alkyl group of α-angelica lactone played an important role for chiral induction. Although the results from experiments provided valuable information for the mechanism as well as selectivity of the asymmetric aldol reaction catalyzed by *N*, *N*′-dioxide-Sc(III) complex, the nature of catalysis and selectivity-controlling were still unclear. Furthermore, theoretical investigation on metallic complex-catalyzed asymmetric direct aldol reaction was very limited. Herein, the reaction mechanism and selectivity of asymmetric direct aldol reaction between isatin and α-angelica lactone (Scheme 1) were investigated by DFT method. The key structural units in the chiral ligand were explored to identify the factors controlling the enantioselectivity as well as diastereoselectivity of the products.

Computational details

All calculations in this work were carried out using Gaussian 09 program package [32]. Geometries were full optimized in the tetrahydrofuran (THF) [31] solvent at the B3LYP [33,34]/6-31G(d,p) level, and characterized by frequency analysis. The self-consistent reaction field (SCRF) method with a polarized continuum model PCM-SMD [35] was adopted to evaluate the effect of solvent. The intrinsic reaction coordinate (IRC) path was traced to check the energy profiles connecting each transition state to two associated minima of the proposed mechanism [36]. Natural bond orbital (NBO) [37] and reactivity indices analysis (electrophilicity index ω and nucleophilicity index N) [38–40] of all optimized structures were performed to obtain further insight into the electronic properties of the system at the same theoretical level. The corresponding local reactive indices (ω_k and N_k) were defined as $\omega_k = \omega P_k^+$ and $N_k = N P_k^-$, where the electrophilic Parr functions P_k^+ and nucleophilic Parr functions P_k^- were calculated from Mulliken atomic spin density (ASD) at the radical anion and the radical cation of the corresponding reagents [41]. To understand the factors affecting the reactivity as well as the selectivity of direct aldolreaction, we performed Activation-strain Analysis (ASM) [42–44] (or distortion/strain model calculation) [45–49] by decomposing bonding energy or activation barrier into the distortion energy (ΔE_{strain}) and interaction energy (ΔE_{int}). Furthermore, the interaction energy between reacting species was further divided into the electrostatic interaction (ΔV_{elstat}), Pauli repulsion (ΔE_{Pauli}), and orbital interaction (ΔE_{oi}) (*i.e.*, $\Delta E_{int} = \Delta V_{elstat} + \Delta E_{Pauli} + \Delta E_{oi}$) by Energy decomposition analysis (EDA) [50].In ASM and EDA calculations, the structures of transition states or intermediates were decomposed into three fragments (*i.e.* isatin (R1), α-angelica lactone (R2) and *N*, *N*′-dioxide-Sc(III) catalyst (CAT)), and each of them was treated in electronic single-spin state. EDA as well as the extended transition state-natural orbitals for chemical valence (ETS-NOCV) [51] calculations were performed by single-point calculations using the Amsterdam Density Functional (ADF) program [52] at the B3LYP/TZP level. Unless specified, the Gibbs free energies of formation (ΔG) corrected by both solvation and zero-point vibrational effects at the B3LYP/6-31G(d,p)(SMD, THF) level under atmospheric pressure and at 298.15 K were used in the discussions.



Scheme 1. Asymmetric direct vinylogous aldol reaction between isatin and α-angelica lactone catalyzed by chiral *N*,*N*′-dioxide-Sc(OTf)$_3$ catalysts.