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A theoretical investigation on the mechanism of the α,α-diphenylprolinol trimethylsilyl ether-catalyzed oxyamination reaction

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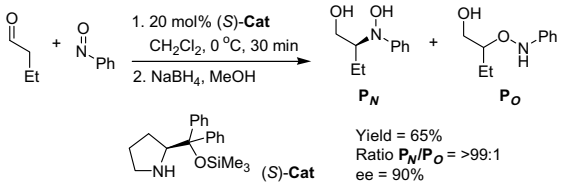
ABSTRACT

A theoretical investigation on the reaction mechanism of a chiral prolinol silyl ether-catalyzed oxyamination reaction strongly suggests that the reaction proceeds via an enol intermediate and not via an enamine intermediate. The catalyst generates the enol and forms an enol-catalyst complex. Nitrosobenzene subsequently reacts with the enol-catalyst complex to afford the (*S*)-*N*-nitroso aldol product. The proposed mechanism is able to account for the experimentally observed enantioselectivity.

The oxyamination reaction is a C–N bond-forming reaction between a nitroso compound and a carbonyl compound, which affords *N*-nitroso aldol products.[1] As nitroso compounds contain two nucleophilic sites (O and N), the aminoxylation reaction, a C–O bond-forming reaction that gives rise to the *O*-nitroso aldol product,[2] will compete with the oxyamination reaction. It is therefore a challenge to develop catalysts that preferentially favor either C–N or C–O bond formation.[3] Recently, Palomo et al.[4] developed a chiral prolinol ether derivative catalyst ((*S*)-**Cat**), and have successfully employed this catalyst in enantioselective oxyaminations (Scheme 1). A higher yield and a higher enantiomeric excess of the *N*-nitroso product were obtained when the reaction was carried out in CH_2Cl_2.

Palomo et al.[4] attempted to rationalize the preference for the (*S*)-*N*-nitroso product isomer via a steric control approach. They made the assumption that the reaction proceeds via an enamine intermediate. Momiyama[5] reported that the TADDOL-catalyzed reaction between preformed enamines and nitrosobenzene affords *N*-nitroso aldol products. The enamine reaction scheme is also extended from the case of the proline-catalyzed aldol reaction,[6] where experimental[7] and theoretical[8] studies seem to support indirectly the enamine pathway. We note here that in the proline-catalyzed aldol reactions, enamine intermediates have never been detected experimentally. List et al.[7a] reported in their NMR studies of the reaction of acetone with proline that they observed the formation of an oxazolidinone and not an enamine.



Scheme 1. (*S*)-**Cat**-catalyzed enantioselective oxyaminations.[4]

The formation of an enamine from amines and aldehydes is known to proceed via an iminium ion. The first step of enamine formation involves C–N bond formation between the carbonyl carbon of the aldehyde and the nitrogen of the amine-catalyst. In the case of the proline-catalyzed aldol reaction, the acidic hydrogen from the carboxylic acid functional group aids in C–N bond formation[8c] (Scheme 2a). An alternative C–N bond formation step, via a 4-center transition state, is known to be higher in energy (Scheme 2b).

As (*S*)-**Cat** does not possess an acidic hydrogen to promote C–N bond formation with the aldehyde that leads to enamine formation, we suspect that this particular reaction may not proceed via an enamine intermediate. Although the $SiMe_3$ group in (*S*)-**Cat** may be considered acidic, the possibility of $SiMe_3$ undergoing a series of shifts seems unlikely. To better understand the role of the prolinol silyl ether catalyst, we report here a MP2/6-311G**//B3LYP/6-31G* (solvation) theoretical investigation of the reaction mechanism of the (*S*)-**Cat**-catalyzed *N*-nitroso aldol reaction between nitrosobenzene and butanal (Scheme 3). Understanding

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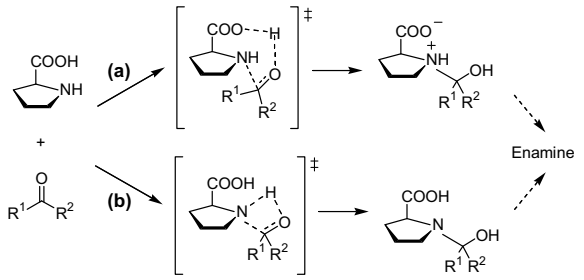
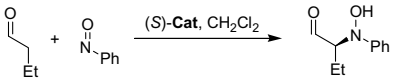


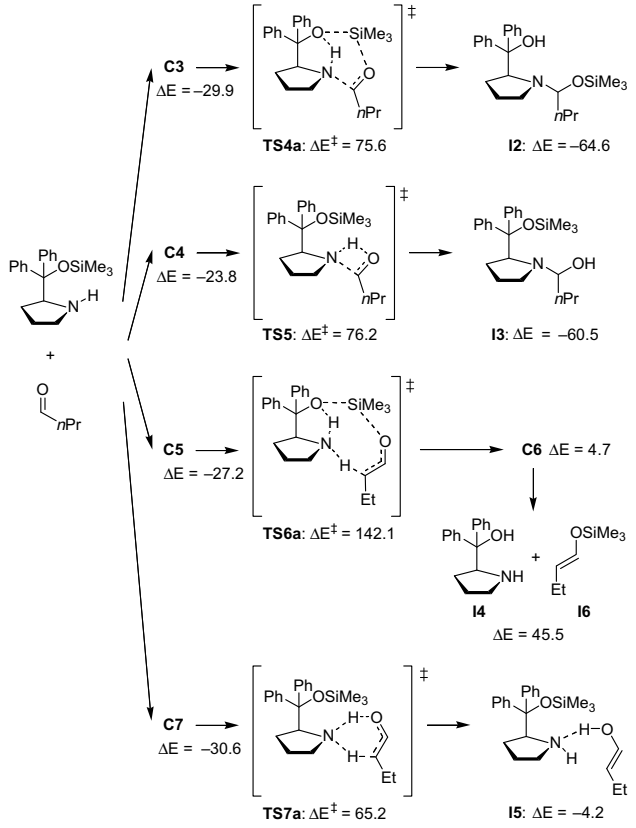
Scheme 2. C–N bond formation steps between a carbonyl compound and proline.



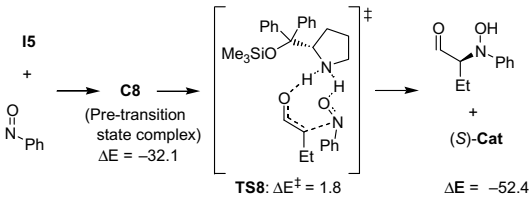
Scheme 3. (*S*)-**Cat**-catalyzed *N*-nitroso aldol reaction between butanal and NOPh.

the reaction mechanism will greatly aid in the design of more efficient enantioselective catalysts.

For the (*S*)-**Cat**-catalyzed oxyamination reaction (Scheme 3), four plausible initial reactions between butanal and (*S*)-**Cat** have been identified (Scheme 4). These reactions correspond to C–N bond formation (**TS4** and **TS5**) and enol formation (**TS6** and **TS7**). The enol formation reaction via **TS7a** has the lowest energy barrier of 65.2 kJ mol^{-1} among the reactions considered. The calculated Gibbs free energies of these four reactions also show a similar reaction profile (Scheme S2: see Supplementary data). **TS7a** corresponds to two simultaneous H-exchanges between butanal and (*S*)-**Cat** to form a *trans* enol, which is favored over *cis* enol formation (via **TS7b**) by 8.9 kJ mol^{-1}. The preference of **TS7** over **TS4**, **TS5,** and **TS6** may be attributed to the acidity of the α-hydrogen of the aldehyde, which facilitates the hydrogen exchanges. Reactions involving ionic species were not considered as (*S*)-**Cat** does not possess any acidic hydrogens.



Scheme 4. Plausible initial reactions between butanal and (*S*)-**Cat**. Calculated energy barriers (Δ$E^{‡}$) and reaction enthalpies (ΔE) correspond to the relative energies with respect to (*S*)-**Cat** + butanal, in kJ mol^{-1}. Structures **C3**, **C4**, **C5,** and **C7** are pre-transition state complexes. Structure **C6** is a product complex.

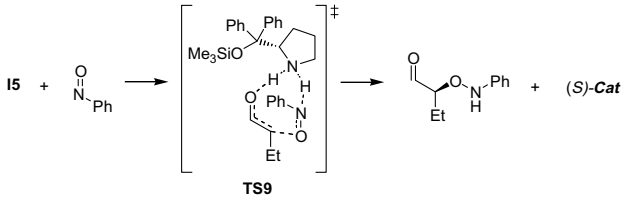


Scheme 5. Formation of the (*S*)-*N*-nitroso aldol product from the reaction between **I5** and NOPh. The calculated energy barrier (Δ$E^{‡}$) and reaction enthalpy (ΔE) correspond to the relative energy with respect to **I5** + NOPh, in kJ mol^{-1}.

Once the *trans* enol is generated via **TS7a**, it immediately forms a complex (**I5**) with (*S*)-**Cat** via hydrogen bonding. Nitrosobenzene subsequently reacts with **I5** from the *Si* face of the enol (via **TS8**) to afford the experimentally observed (*S*)-*N*-nitroso aldol product (Scheme 5). The energy barrier for **TS8** is calculated to be 1.8 kJ mol^{-1}. **TS8** consists of simultaneous (i) C–N bond formation between the enol and nitrosobenzene, (ii) a H-shift from the O of the enol to N of (*S*)-**Cat**, and (iii) a H-shift from N of (*S*)-**Cat** to O of nitrosobenzene. The stereochemical orientation of the hydrogen that undergoes H-shift (iii) dictates that nitrosobenzene has to approach from the *Si* face of the *trans* enol moiety in **I5**. (Fig. S1: see Supplementary data).

The transition state (**TS9**) calculated for C–O bond formation between **I5** and nitrosobenzene to afford the *O*-nitroso aldol product (Scheme 6) is 6.4 kJ mol^{-1} (Gibbs free energy value) higher in energy than **TS8** (Scheme S3: see Supplementary data), which is in agreement with the experimentally observed C–N selectivity over C–O selectivity. Charge analysis of **I5** and nitrosobenzene suggests that the preference for C–N selectivity may be attributed to the electrostatic attraction between the C of the enol moiety in **I5** and the N of nitrosobenzene (Fig. 1).

Our calculations strongly suggest that the reaction mechanism of the (*S*)-**Cat**-catalyzed *N*-nitroso aldol reaction between nitrosobenzene and butanal proceeds via an enol intermediate and not



Scheme 6. Formation of the *O*-nitroso aldol product from the reaction between **I5** and NOPh.

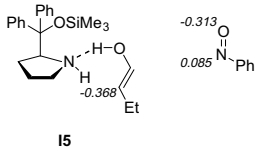


Figure 1. Calculated natural bond orbital (NBO) charges for selected atoms in **I5** and NOPh.

via an enamine intermediate. The functions of (*S*)-**Cat** are (i) it assists in the formation of an enol via H-exchanges and (ii) it forms a complex with a *trans* enol, the enol-catalyst complex assists in controlling the stereochemistry at the α-position of the aldol as *S*. Our proposed enol mechanism accounts for the experimentally observed C–N selectivity and enantioselectivity. We predict that pyrrolidine will be able to catalyze the oxyamination reaction shown in Scheme 3 (calculated energy barrier for proton exchange to form the *trans* enol = 79.2 kJ mol^{-1}).

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Supplementary data

Theoretical methods, uncatalyzed reactions, Si selectivity, Gibbs free energies of key reaction pathways, conformational flexibility of intermediates and transition states, Cartesian coordinates and absolute energies of all compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.012.

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