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Origin of Regioselectivity in Electrophilic Reaction of Ambident Enaldimines

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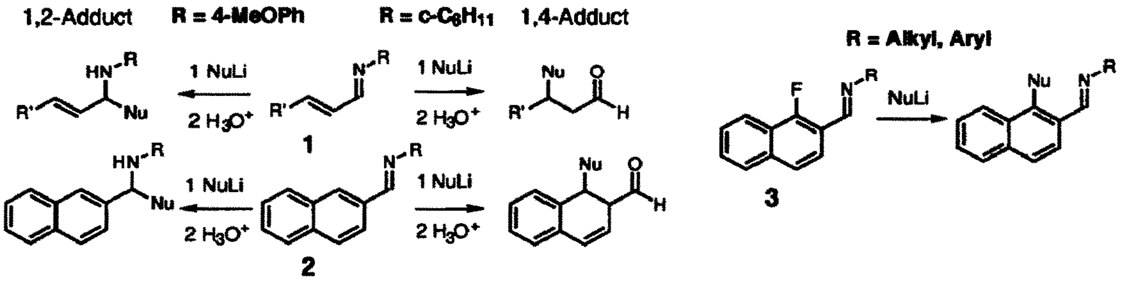
Abstract: *The observed substituent-dependent regioselectivity (1,2- vs 1,4-addition) in the electrophilic reaction of ambident imines 1-3 is rationally understood by the relative magnitude of the LUMO coefficients of the imines.*

We have recently reported the successful chiral ligand-mediated asymmetric 1,2- and 1,4-addition reactions of organolithiums to various imines of aryl and α,β-unsaturated aldehydes.[1] Thus, organolithiums add to the cyclohexylimines **1**, **2** (R=c-C_6H_{11}) in 1,4-fashion to give, after hydrolysis, the corresponding aldehydes in up to 99% ee and in high to good yields.[2] On the other hand, the reactions with arylimines **1**, **2** (R=4-MeOPh) exclusively afford 1,2-adducts in up to 90% ee and in nearly quantitative yields, giving us a good method for the preparation of chiral amines.[3,4] It is also interesting in that the reactions with both cyclohexyl- and arylimines of 1-fluoronaphthalene-2-carbaldehyde **3** exclusively proceed in 1,4-fashion to provide nucleophilic aromatic substitution products in high yields.[5] Since deep understanding of the factors governing regioselectivity is a long-standing problem[6,7] and essential for further development of the much more effective catalytic asymmetric reactions of the ene-imines, we carried out molecular orbital calculations of **1-3**.[8]



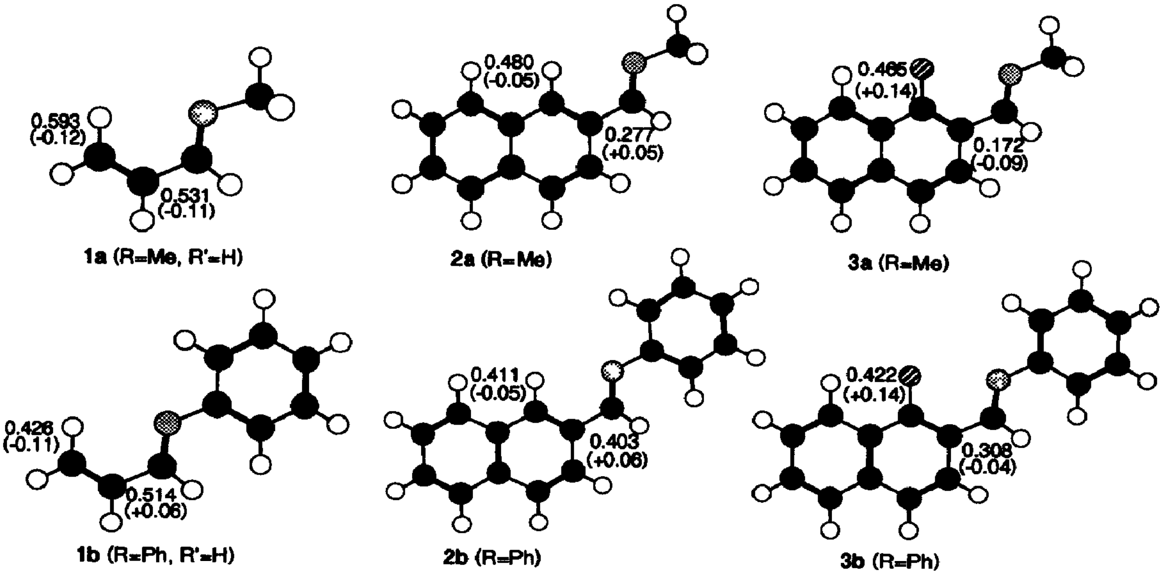
All *s-cis* and *s-trans* structures **1**,**2** were fully optimized with the ab initio (HF/STO-3G) method under the Cs constraint. PM3 optimization (precise mode) for **1-3** (*s-cis*) and HF/3-21G for **2b** (R=Ph, *s-cis*) were also carried out for comparison. The optimized geometries of *s-cis* conformation are shown in the **Figure I** together with the absolute values of the LUMO coefficients and the total charges (in parentheses) at the each reaction site (2- and 4-positions).

Comparison between **1a** (R=Me, R'=H) and **1b** (R=Ph, R'=H) revealed that the experimentally observed regioselectivity is rationalized by the relative magnitude of the LUMO coefficients. The arylimine **1b** has a much larger coefficient at the 2-position than the 4-position, consistent with the exclusive 1,2-addition for **1b**,[3] while the coefficient is larger at the 4-position for the alkylimine **1a**, for which the 1,4-adduct is the major product.[2] Similarly, the 4-position has a much larger coefficient than the 2-position for the alkylimine **2a** (R=Me), which gave only the 1,4-adduct, the product thermodynamically less stable than the 1,2-adduct due to the breakdown of the naphthalene aromaticity. In contrast, the size of the LUMO coefficient is similar at the 2- and 4-positions for the arylimine **2b** (R=Ph), for which the 1,2-addition is the preferred reaction,[3] probably due to the aromaticity.

Results for the *s-trans* isomers are nearly the same as *s-cis*, and the difference in the method of calculation (HF/3-21G, HF/STO-3G, and PM3) has little influence on a qualitative conclusion. The reason for the substituent-dependent reversal of the LUMO coefficient magnitude is probably ascribable to the electron withdrawing and donating nature of the aryl and alkyl groups, respectively.

PM3 calculations for **3a**,**b** (R=Me, Ph) revealed the larger coefficient at the carbon attached to fluorine than that at the imine carbon, indicating the experimentally observed S_NAr reaction.[5]

Thus, it became clear that the relative magnitude of the LUMO coefficient is one of the major factors governing the substituent-dependent regioselectivity of the ambident ene-imines. Based on the result, further efforts toward much more effective asymmetric reactions by varying imine-substituents are in progress in our laboratories.[9]



1a (R=Me, R'=H) **2a** (R=Me) **3a** (R=Me)

1b (R=Ph, R'=H) **2b** (R=Ph) **3b** (R=Ph)

Figure I. Optimized geometries (Chem3D presentation), LUMO coefficients and total charges (in parentheses) at the reaction sites of **1**-**3**.

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