



Role of substituents in Hofmann-Löffler-Freytag cyclization of biomolecules. A quantum chemical study



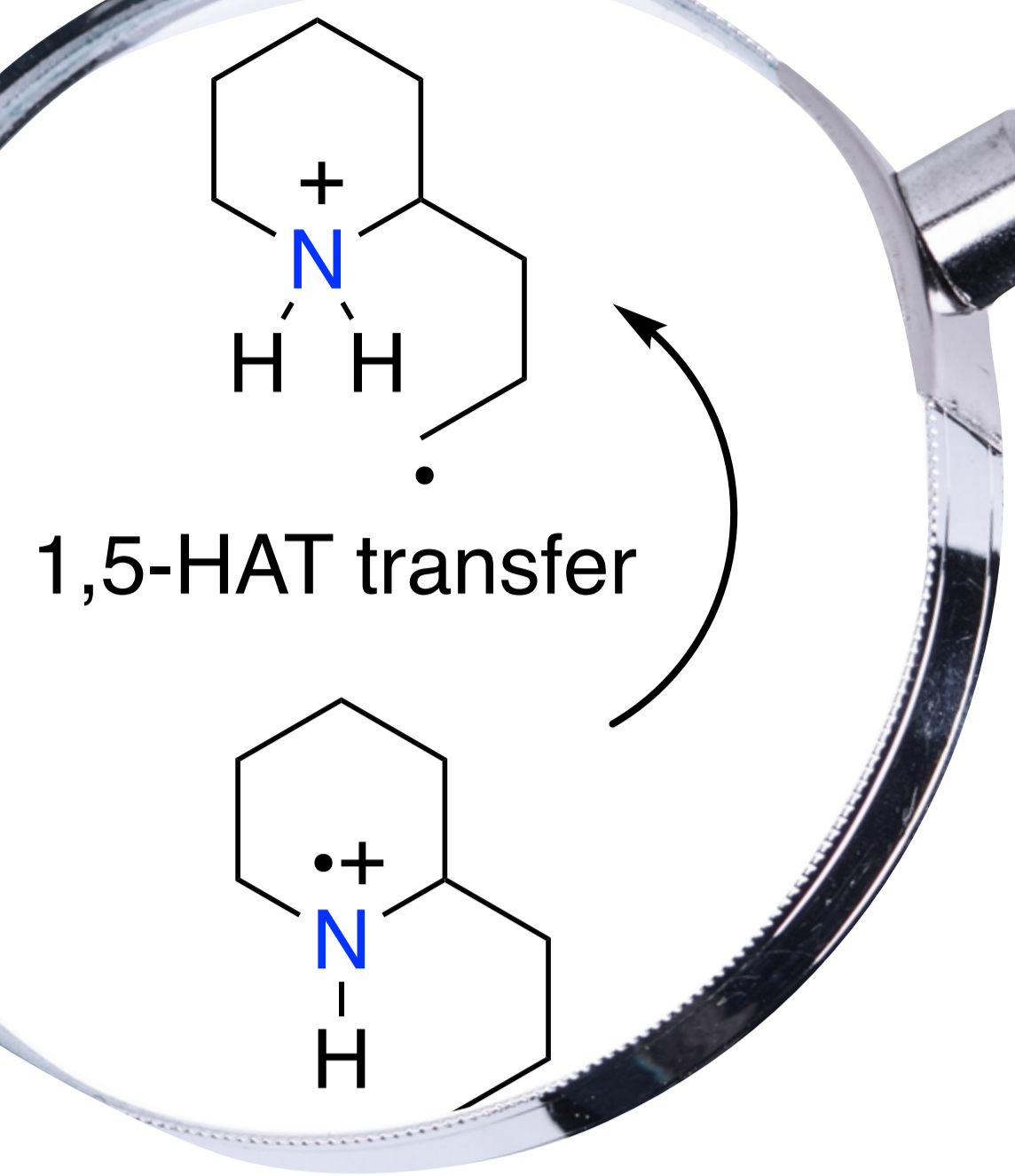
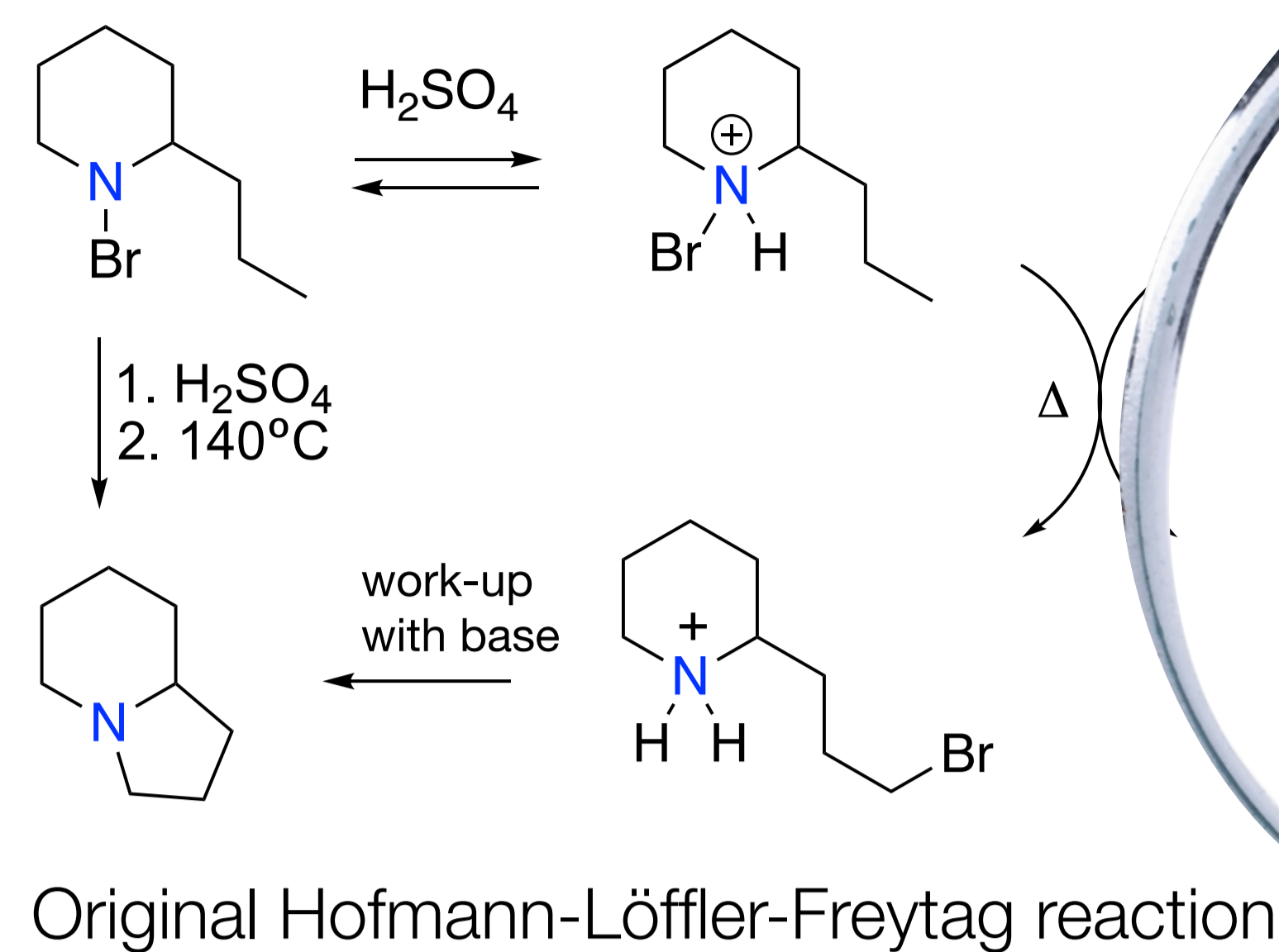
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Efficient Method for Selective Introduction of Substituents as C(5) of Isoleucine and Other α -Amino Acids

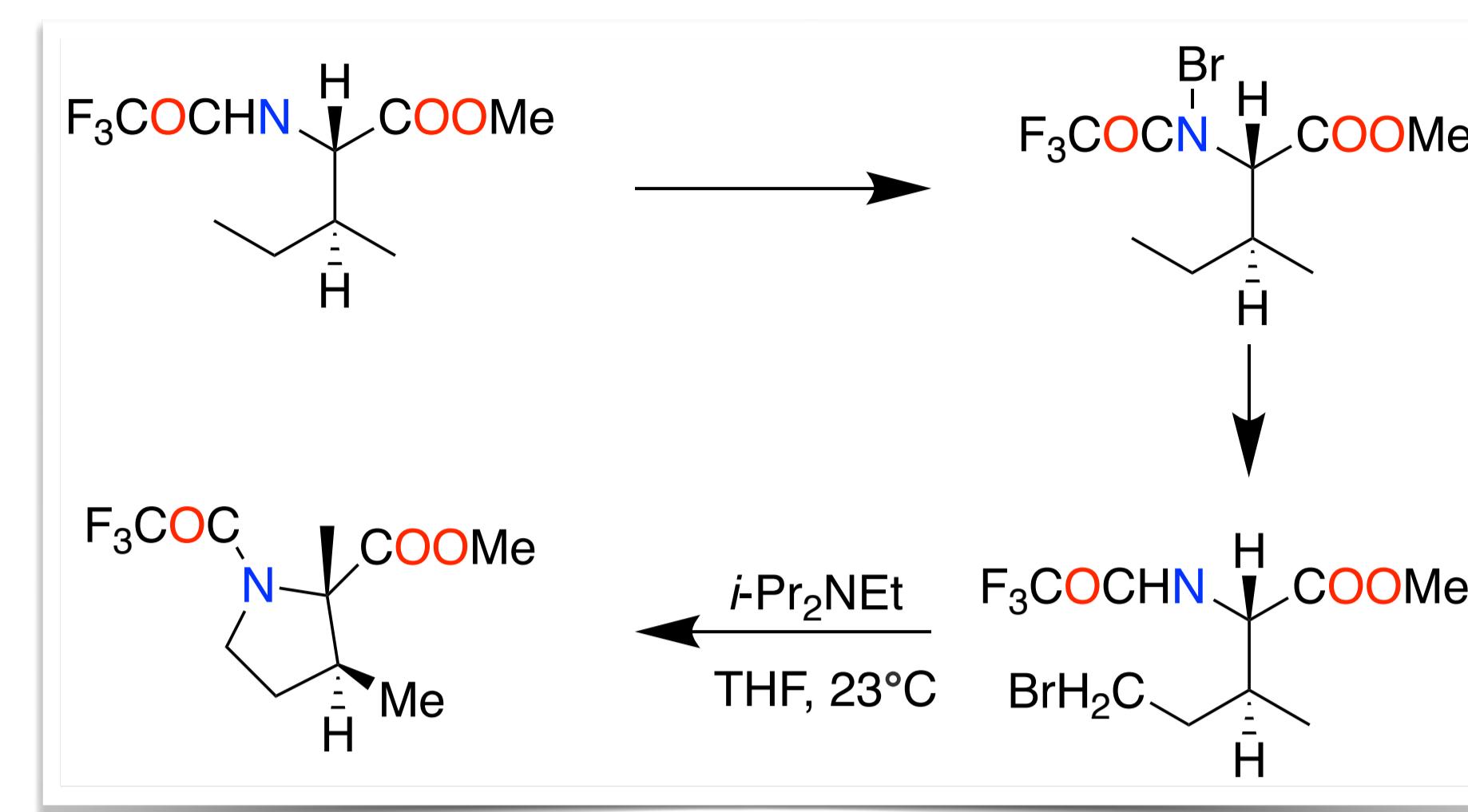
Leleti Rajender Reddy, B. V. Subba Reddy, and E. J. Corey*

ORGANIC LETTERS

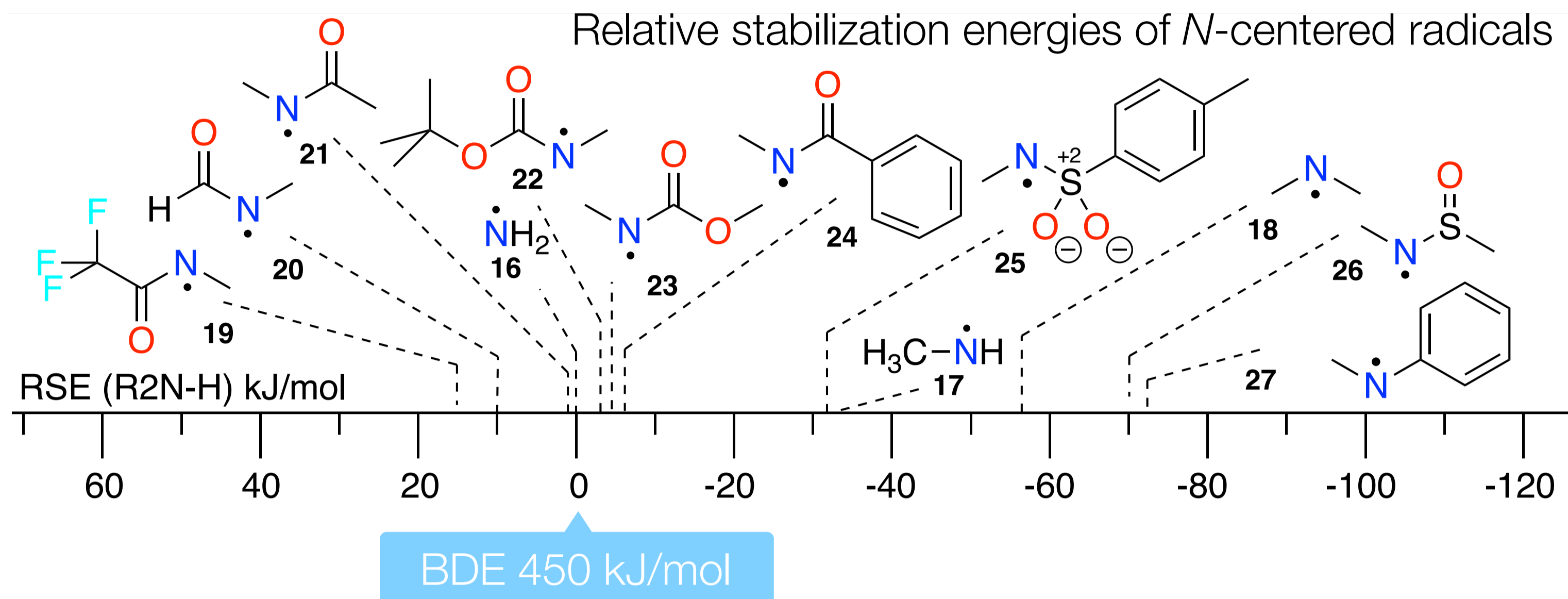
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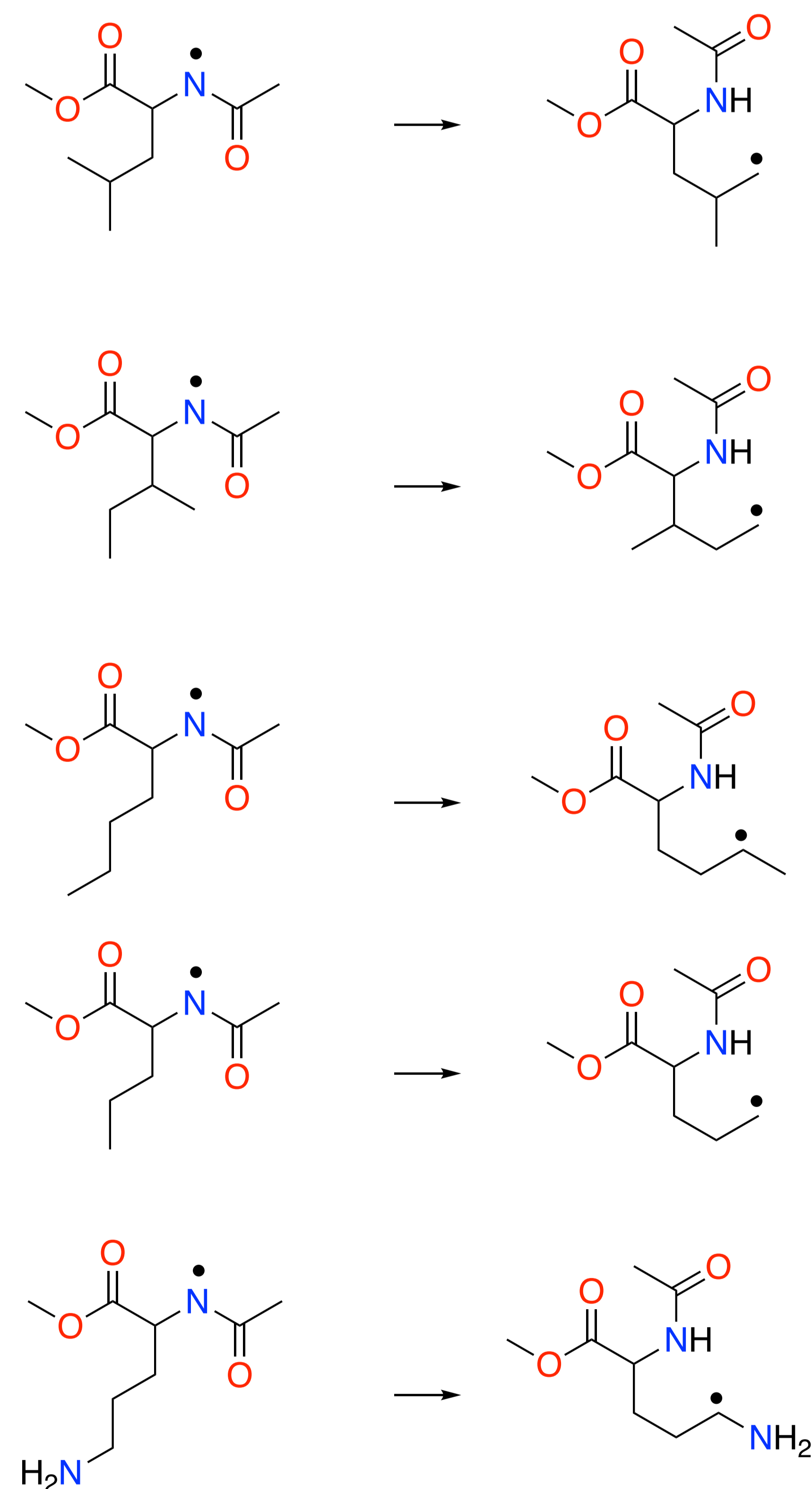
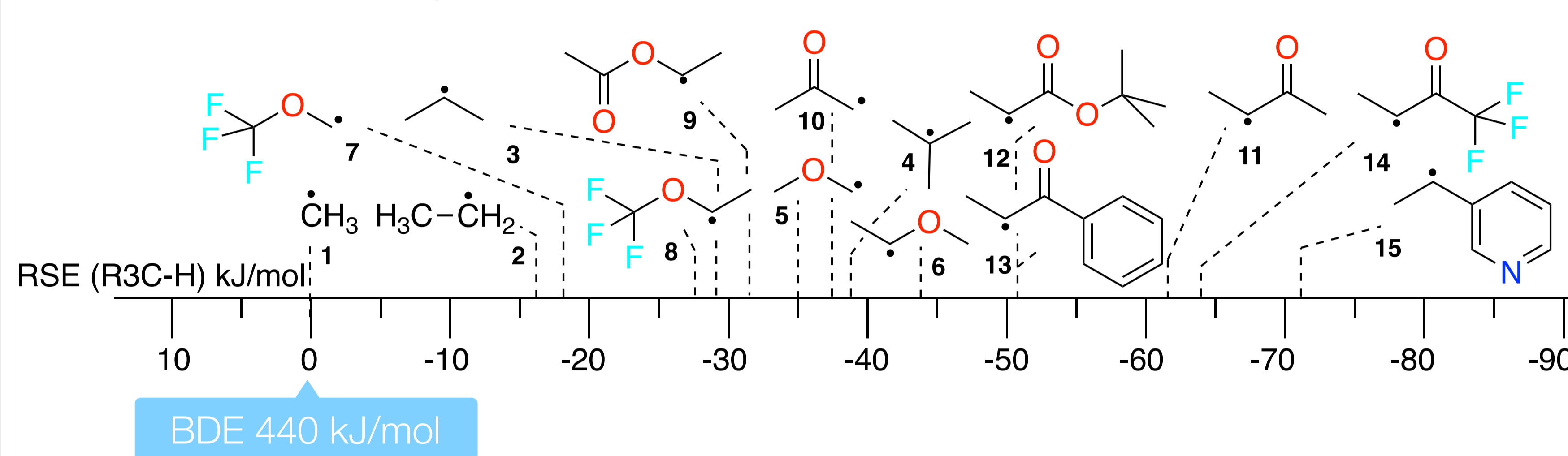
The search for amination reactions of the C-H bond in metal-free conditions has recently led to a resurgence in studies of the Hofmann-Löffler-Freytag (HLF) reaction and its modern variants. Crucial step in the HLF reaction pathway is hydrogen atom transfer (HAT) from the N-centered radical to C-centered radical. Reddy and Corey used α -amino acids for the synthesis of useful chiral substances which can be used for the discovery of new bioactive substances. Here we try to understand possible biological applications of radical rearrangements in peptide models.



Relative stabilization energies of N-centered radicals



Relative stabilization energies of C-centered radicals



	ΔH_{rx} kJ/mol	ΔH^\ddagger kJ/mol
Leucine	-38.30	31.31
Isoleucine	-41.58	23.35
Norleucine	-54.06	21.47
Norvaline	-37.16	36.05
Lysine	-79.67	22.27

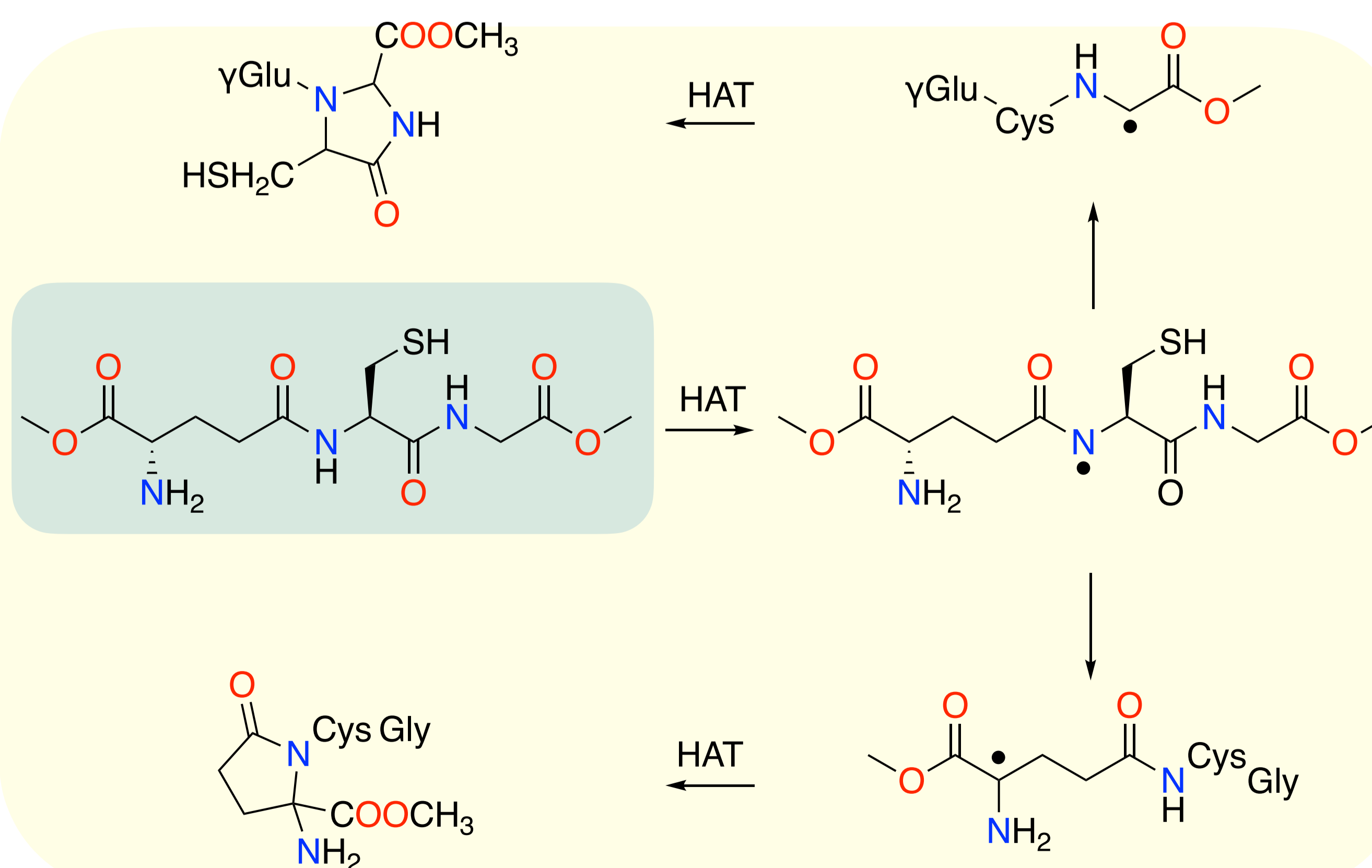
	ΔH_{rx} kJ/mol	ΔH^\ddagger kJ/mol
Valylglycine	-39.41	33.65
Serylglycine	-24.60	31.71
Cysteinylglycine	-95.34	16.19
Methionylglycine	-85.48	3.01
Glutamylglycine	-86.34	38.87

- All reactions are exothermic
- Small barriers, and fast reactions
- Preference for 5-membered rings

When species with oxidative properties, such as HOCl, are found inside a cell, open-shell species may be formed. We have shown that on various N-centered radicals that are formed from amino acids, dipeptides and glutathione by homolytic cleavage of a covalent bond. The formed N-centered radical then undergoes a transformation to form a C-centered radical. The formed highly reactive species have low chemical specificity, meaning they can attack most biomolecules, such as nucleic acids or proteins, or form cyclic metabolites, e.g. proline is a product of cyclization of norvaline. All hydrogen atom transfer reactions happen through a 6-membered transition state as shown on picture top.

Case study:

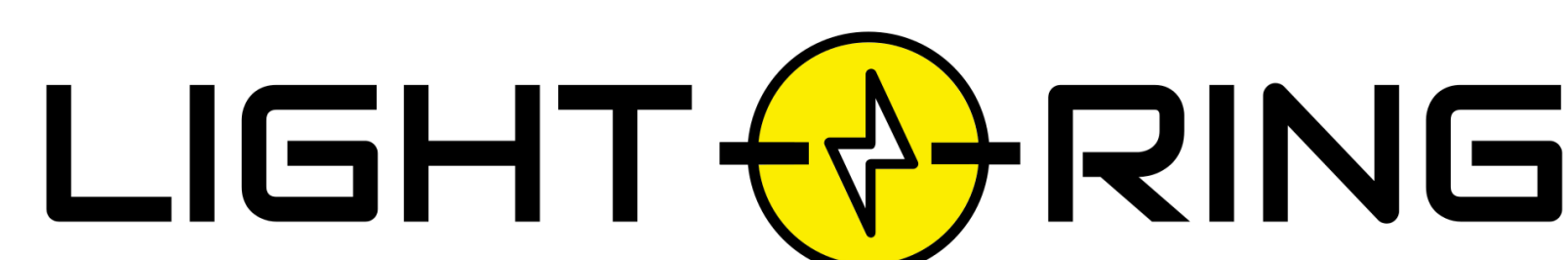
Glutathione (GSH) is a principal antioxidant in living organisms. It acts by forming GSSG by forming a disulfide bond between two GSH molecules. However, if a strong oxidant is present, GSH can form N-centered radical that can convert into two different C-centered radicals with the thiol group intact and available for its role as antioxidant.



- GaussView & Gaussian 16
- geometry optimisation, frequency and IRC calculations @B3LYP/6-31G(d)
- conformation analysis: PCMODEL 10 software
- single point energies @ROB2-PLYP/G3Large
- Cluster Isabella @SRCE

- K. Löffler, S. Kober, *Chem. Ber.*, **1909**, 42, 3431
- E. Del Castillo, K. Muniz, *Org. Lett.*, **2019**, 21(3), 705
- L. R. Reddy, B. V. Subba Reddy, E. J. Corey, *Org. Lett.*, **2006**, 8(13), 2819
- D. Šakić, H. Zipse, *Adv. Synth. Catal.*, **2016**, 358, 3983
- J. Hioe, D. Šakić, V. Vrček, H. Zipse, *Org. Biomol. Chem.*, **2015**, 13, 157
- Lai, W., Li, C., Chen, H., Shaik, S. *Angew. Chem. Int. Ed.*, **2012**, 51, 5556
- Bell, R. P. *Proc. R. Soc. London, Ser. A*, **1935**, 154, 414
- Evans, M. G., Polanyi, M. J. *Chem. Soc., Faraday Trans.*, **1936**, 32, 1340
- Shkunnikova, S., Zipse, H., Šakić, D. *Org. Biomol. Chem.*, **2021**, 19, 854
- Gaussian, Inc., Wallingford CT, **2016**.
- Klaster Isabella, **2007**, <http://www.srce.hr/isabella>

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