



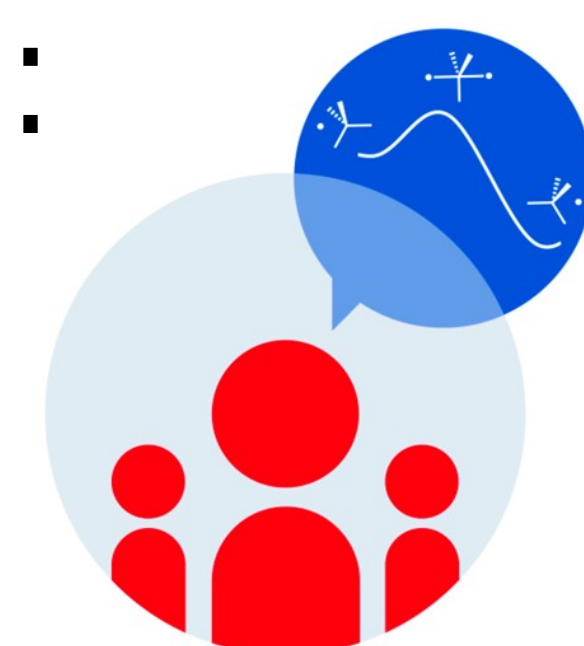
Regioselectivity in the Hofmann–Löffler–Freitag Reaction: A Computational Analysis of Rearrangement Reactions

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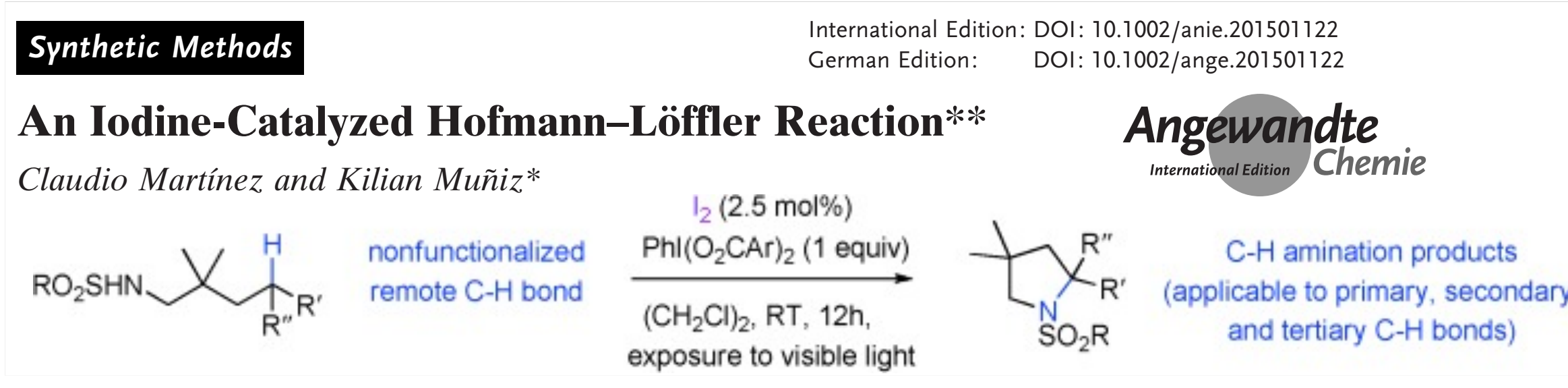
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INTRODUCTION:

Hofmann–Löffler–Freitag (HLF) reaction has seen a resurgence in interest due to shift from metal-based catalysis to organo-catalysis. Recent one-pot approach requires hypervalent iodine oxidant combined with source of iodine (I₂ or NaI) generates in situ halogenating reagent. Homolytically cleaved N-halogen bond under visible light produces N-centered radicals that rearrange to a more stable C-centered radical via 1,5-HAT. This well described process produces predominately pyrrolidine, while trace amounts of piperidine is formed via competing 1,6-HAT. Regioselective synthesis of piperidine is usually done when C5 position is blocked, or when C6 position provides greater thermodynamic driving force.



N-tosyl-hexylamine

		ΔH_{298}^\ddagger	$\Delta H_{rx,298}$	
	START	kJ/mol	kJ/mol	FINAL

1,5-HAT_{NC} N-rad 40.4 -9.3 C5-rad

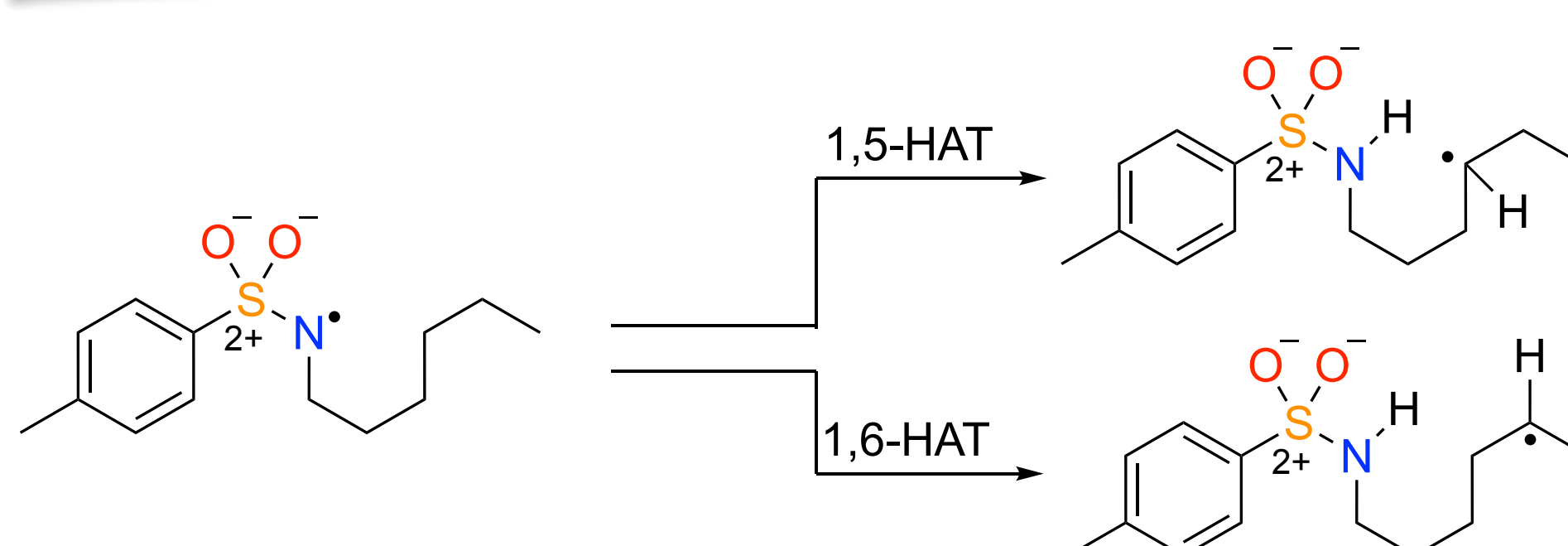
1,6-HAT_{NC} N-rad 40.4 -8.7 C6-rad

Two processes are indistinguishable. Both pyrrolidine and piperidine should be formed

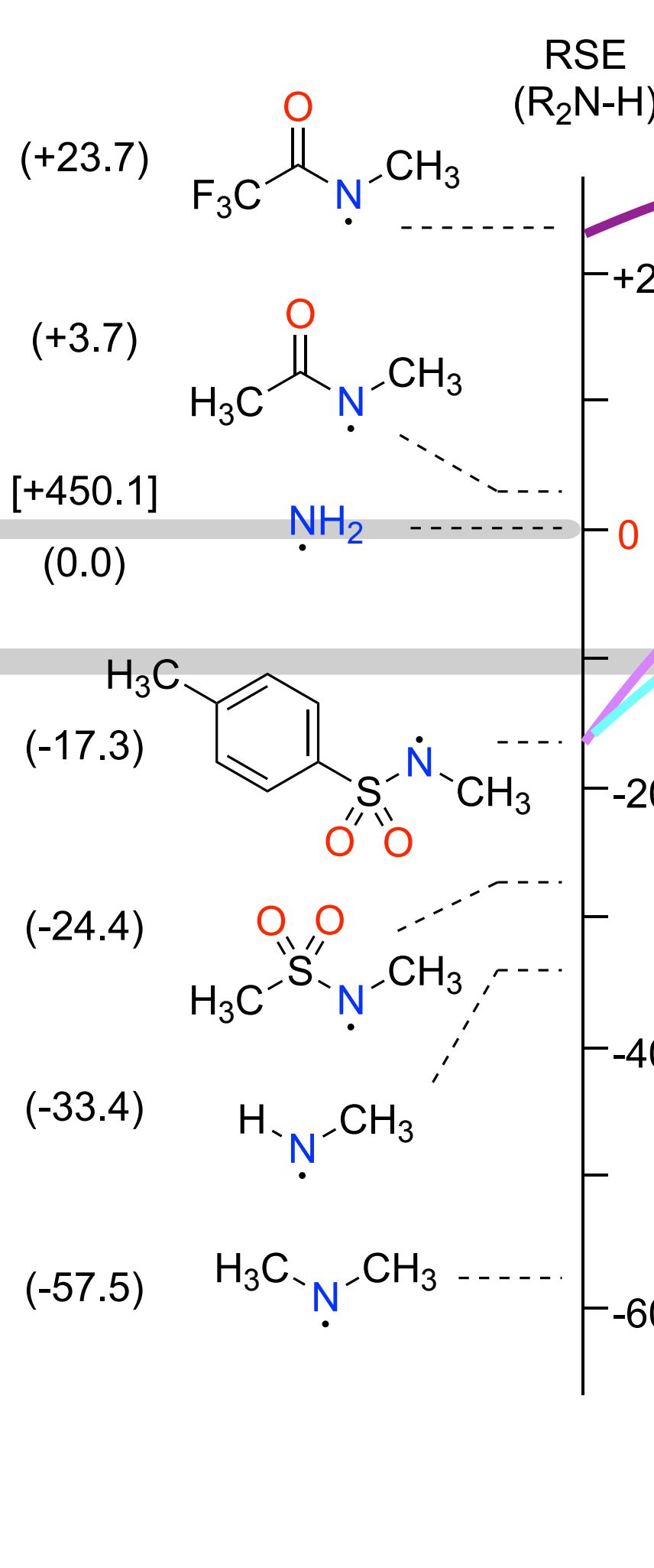
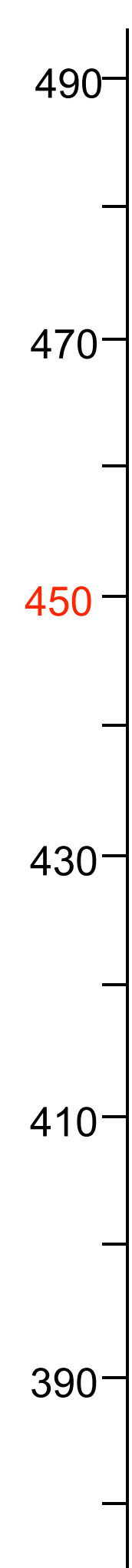
1,2-HAT_{NC} N-rad 153.2 -20.3 C2-rad

1,5-HAT_{CC} C6-rad 57.4 -22.5 C2-rad

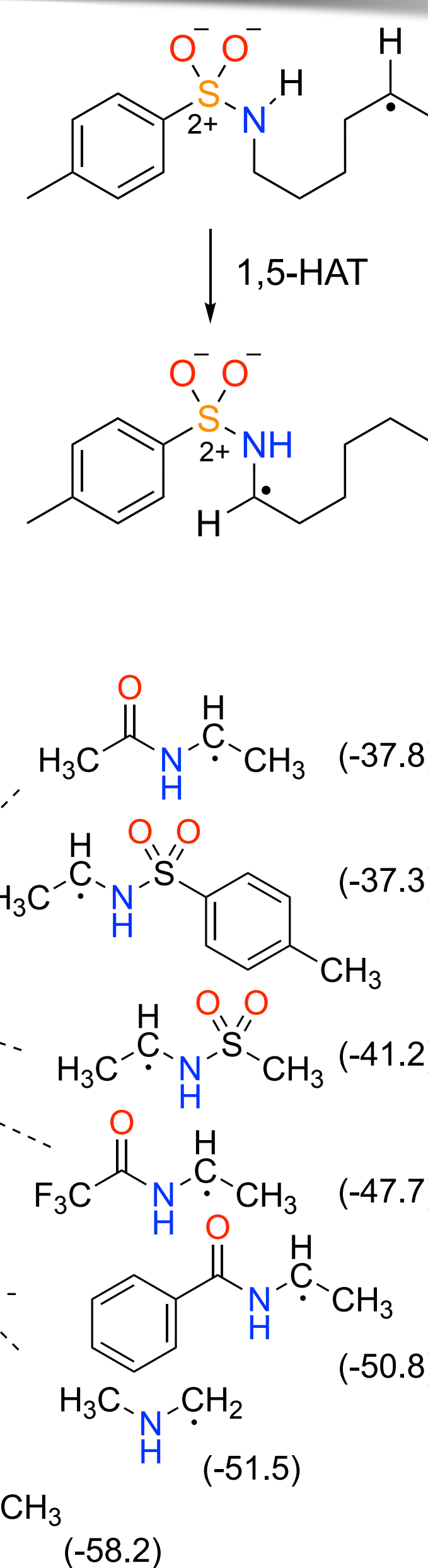
1,4-HAT_{CC} C5-rad 111.2 -21.9 C2-rad



BDE(N-H)
[kJ/mol]



C6-centered radical rearranges to a more favourable C2-centered radical



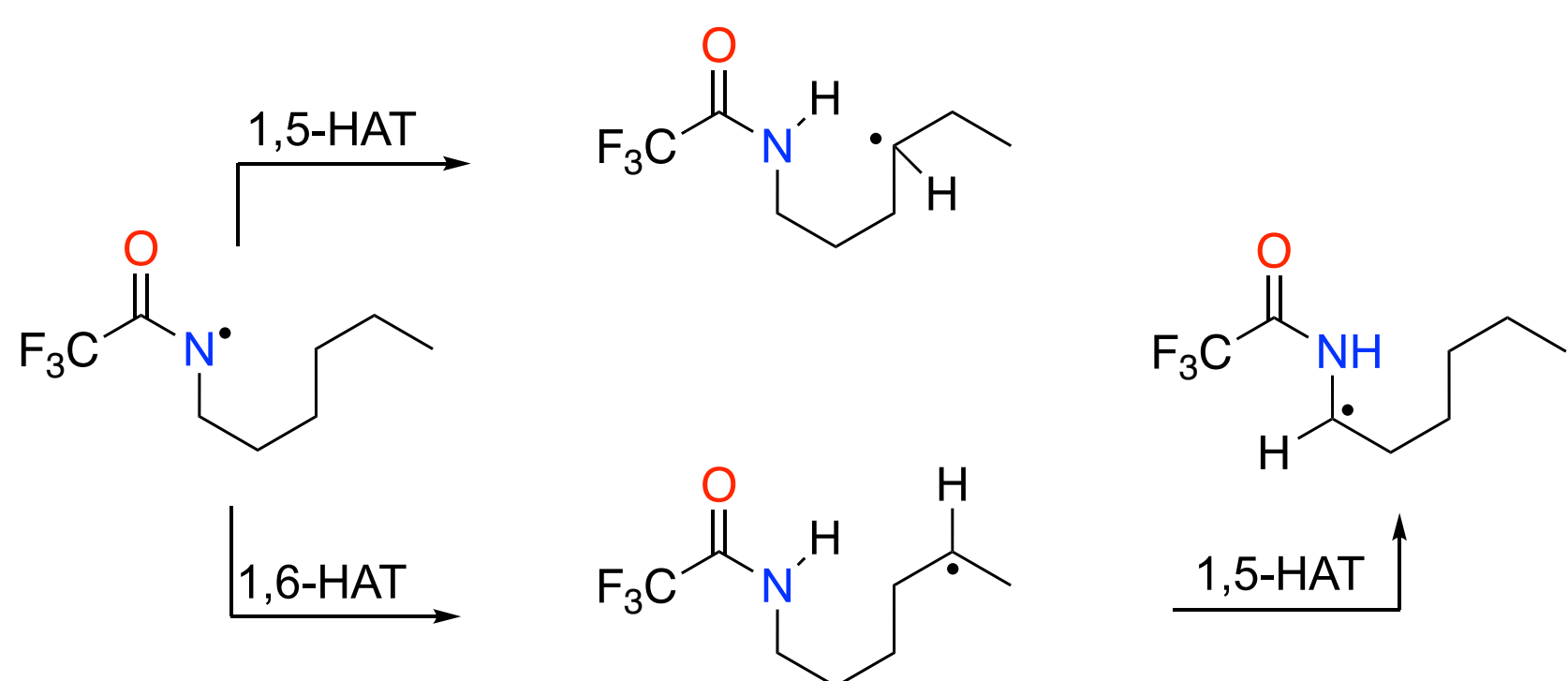
N-trifluoroacetyl-hexylamine

		ΔH_{298}^\ddagger	$\Delta H_{rx,298}$	
	START	kJ/mol	kJ/mol	FINAL

1,5-HAT_{NC} N-rad 36.6 -37.9 C5-rad

1,6-HAT_{NC} N-rad 38.0 -30.3 C6-rad

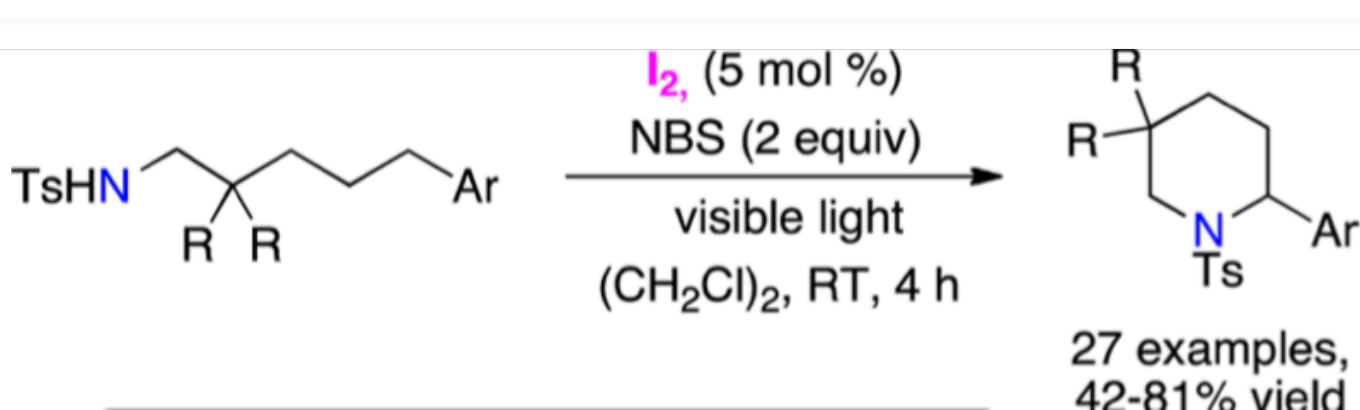
1,5-HAT_{CC} C6-rad 57.6 -15.5 C2-rad



ACS Catalysis

Selective Piperidine Synthesis Exploiting Iodine-Catalyzed C_{sp}³-H Amination under Visible Light

Hongwei Zhang[†] and Kilian Muñiz^{*,†,‡}



- selective piperidine formation
- benign light induced reaction
- radical C-H functionalization
- iodine-catalyzed C-N bond formation

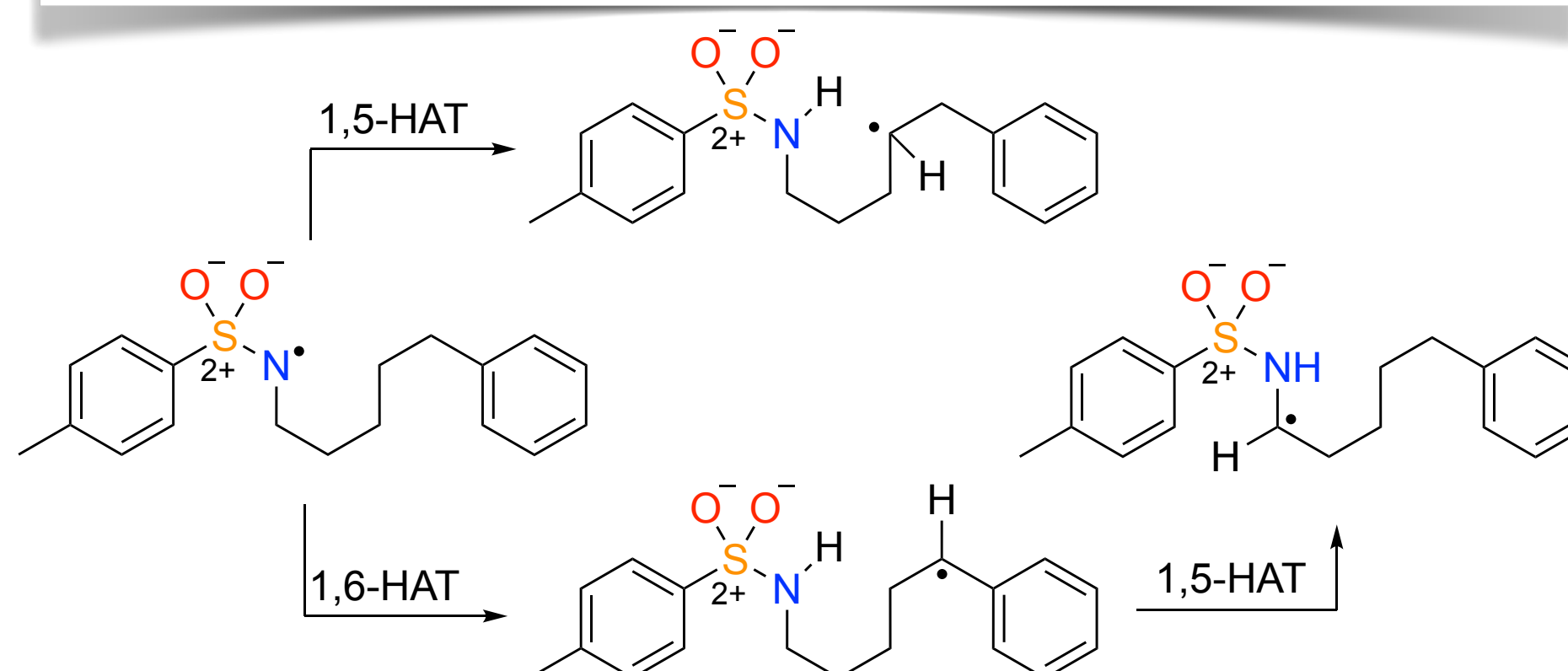
N-tosyl-(5-phenyl)hexylamine

		ΔH_{298}^\ddagger	$\Delta H_{rx,298}$	
	START	kJ/mol	kJ/mol	FINAL

1,5-HAT_{NC} N-rad 58.9 -13.3 C5-rad

1,6-HAT_{NC} N-rad 40.0 -44.2 C6-rad

1,5-HAT_{CC} C6-rad 88.1 25.0 C2-rad



CONCLUSIONS

- pyrrolidine (1,5-HAT) and piperidine (1,6-HAT) pathways are kinetically and thermodynamically indistinguishable
- location of the most stable radical in the molecule
- molecular fragments can be used in prediction
- C6 radical may rearrange to more stable C2 radical via 1,5-HAT
- probable reason for pyrrolidine product
- radical stabilities play crucial role in determination of products

METHODS

- IQmol, GaussView & Gaussian 16
- geometry optimisation, frequency and IRC @B3LYP/6-31G(d)
- conformation analysis: XTb-GFN2
- single point energies @B2-PLYP-D3/G3MP2Large
- Cluster Isabella & HR-ZOO SUPEK @SRCE.hr & SW @PHARMA.hr

LITERATURE

- J. Hioe, D. Šakić, V. Vrčec, H. Zipse, *Org. Biomol. Chem.*, **2015**, *13*, 157
- D. Šakić, H. Zipse, *Adv. Synth. Catal.*, **2016**, *358*, 3983
- S. Shkunnikova, H. Zipse, D. Šakić, *Org. Biomol. Chem.*, **2021**, *19*, 854
- C. Martínez, K. Muñiz, *Angew. Chem.*, **2015**, *54*(28), 8287-8291
- H. Zhang, K. Muñiz, *ACS Catal.* **2017**, *7*, 4122-4125



LIGHT RING

HRZZ project UIP 2020-02-4857