C-H amination reactions via radical pathway; repurposing Hofmann-Löffler-Freytag reaction.

Gabrijel Zubčić, Marijan Marijan, Davor Šakić

University of Zagreb

Faculty of pharmacy and biochemistry

Ante Kovačića 1, 10 000 Zagreb

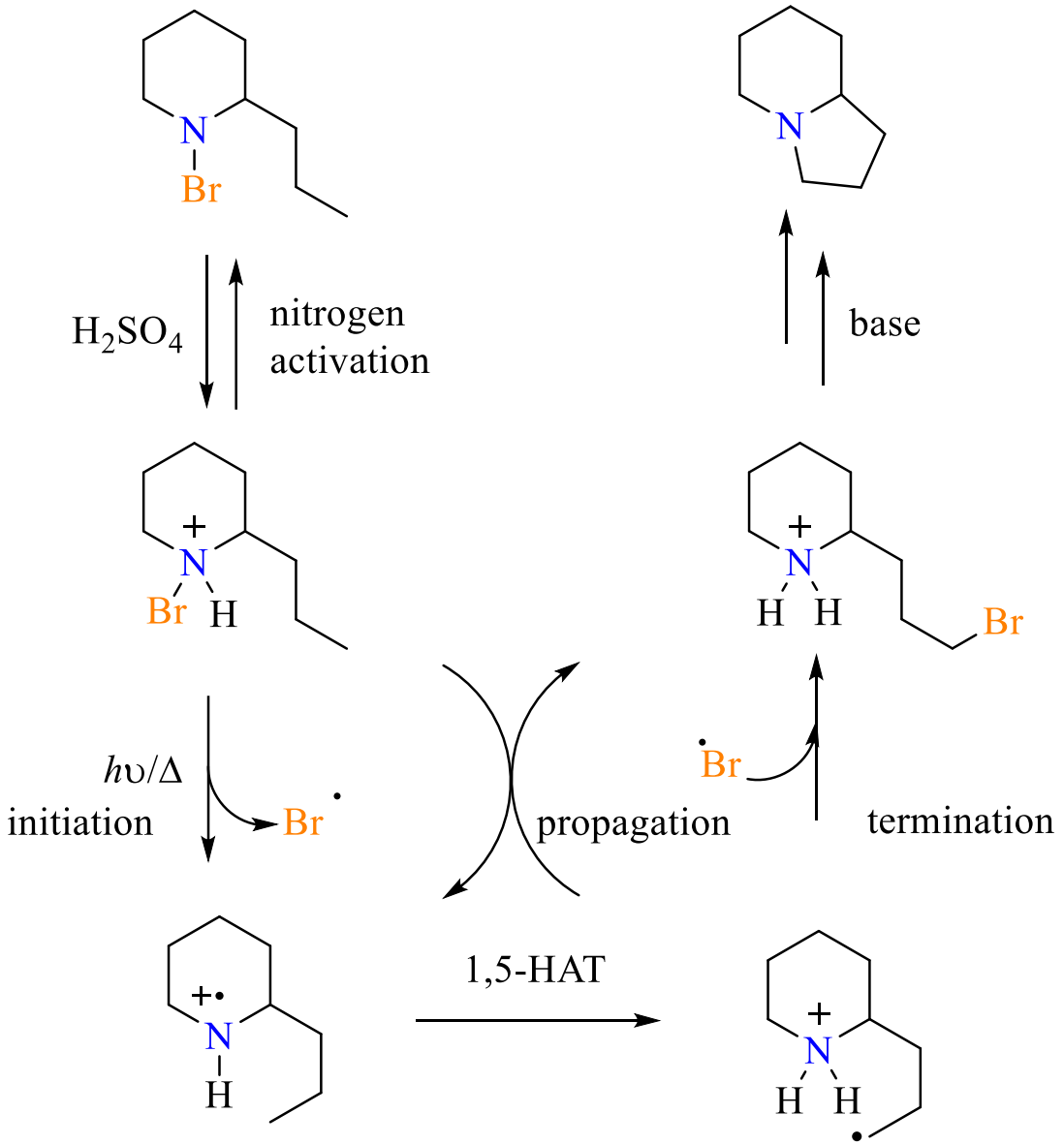
LIGHT RING

HrZZ Croatian Science Foundation

Hofmann-Löfller-Freytag reaction

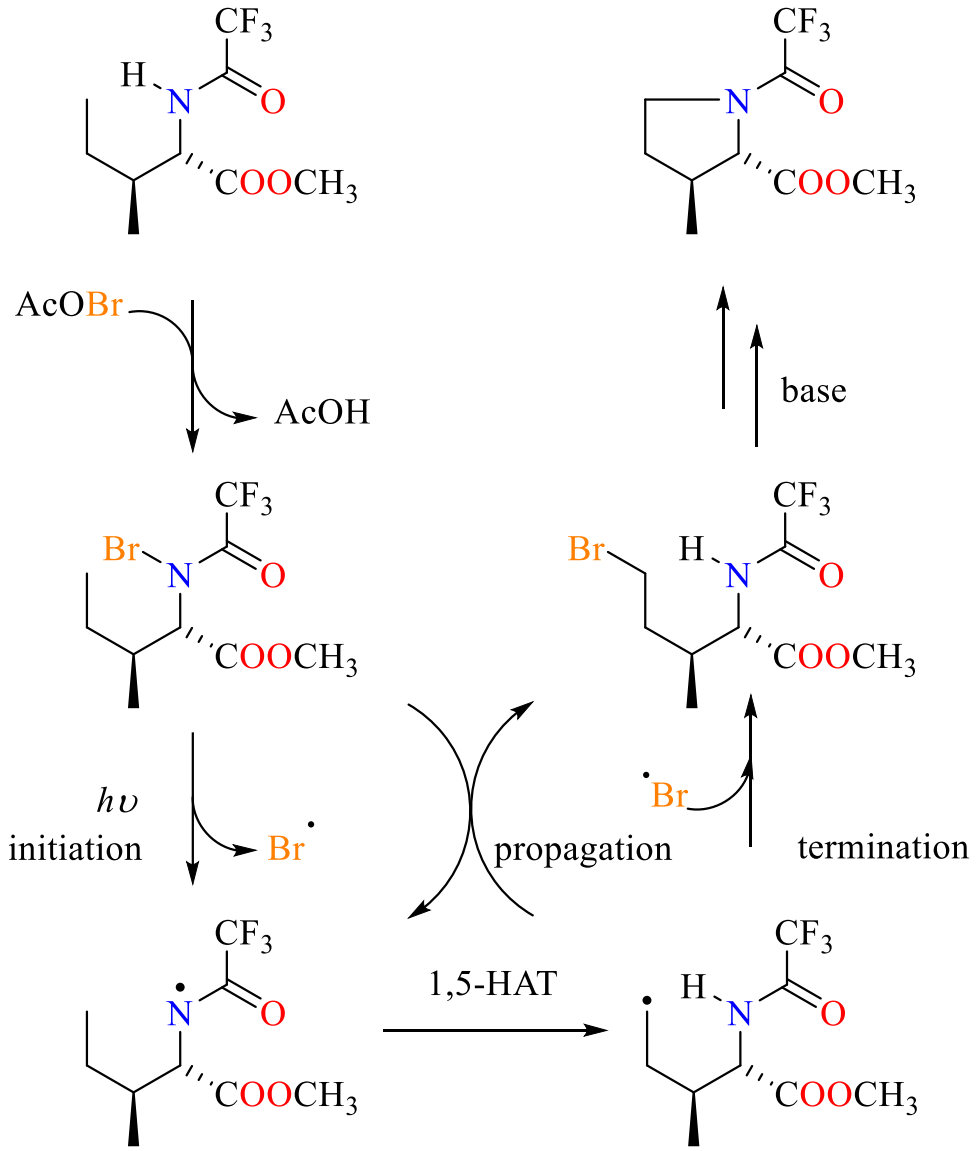
- Tool inside the C-H functionalization toolbox
- Product of the reaction is pyrrolidine and more sparsely piperidine
- It is defined as a late stage functionalization synthetic strategy
- Has the potential to become an organo-catalysed reaction in mild conditions in keeping with green chemistry principles

Original Hofmann-Löfller-Freytag (HLF) reaction



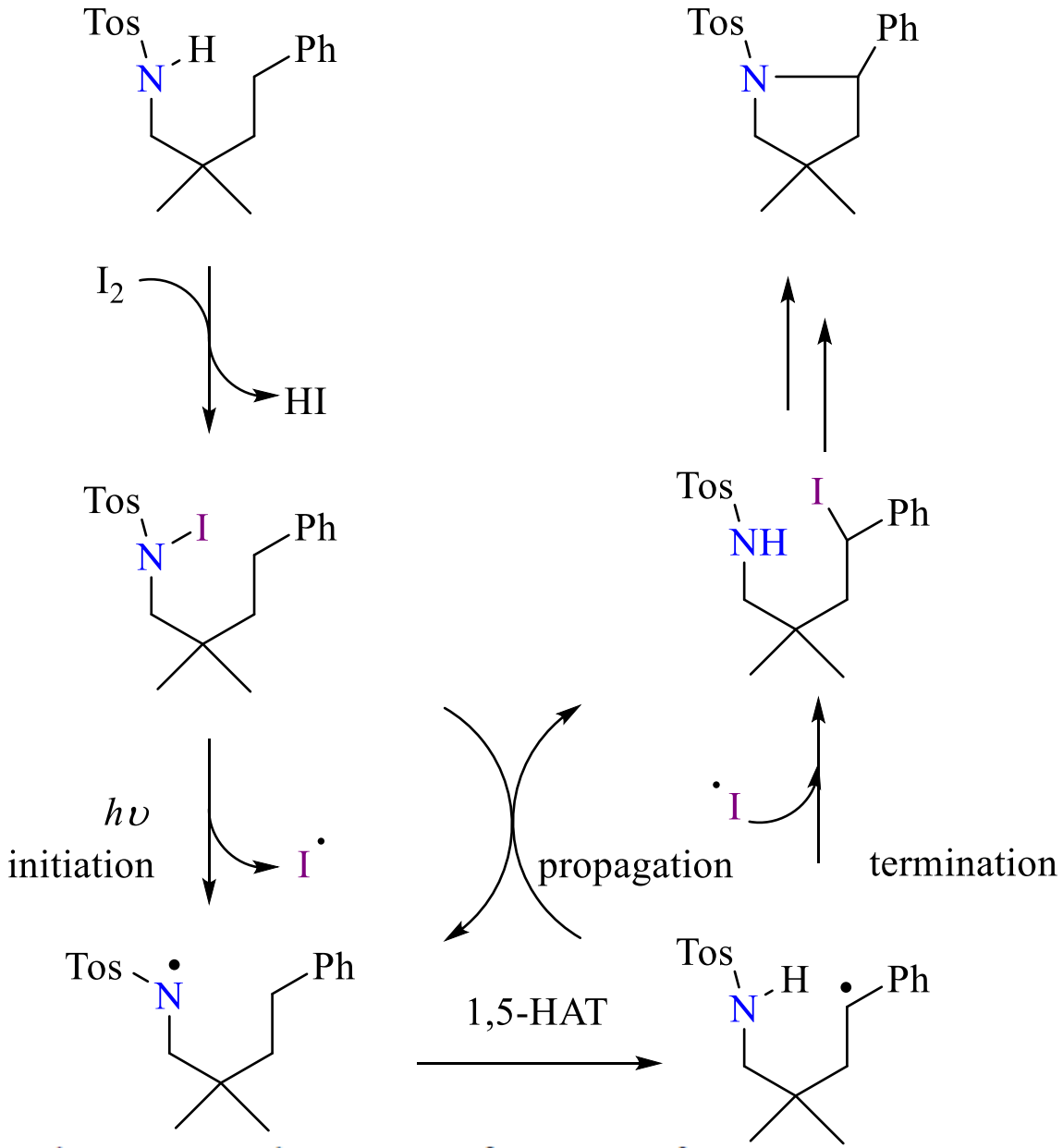
a) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1881**, 14, 2725; b) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1883**, 16, 558; c) Hofmann, A. W. *Ber. Dtsch. Chem. Ges.* **1885**, 18 (5), 109 d) Löffler, K., Freytag, C. *Ber. Dtsch. Chem. Ges.* **1909**, 42, 3427

"Corey modification" of the HLF procedure



Reddy, L. R., Reddy, B. V. S., Corey, E. J. *Org. Lett.* **2006**, *8*, 2819 – 2821.

"Suarez modification" of the HLF reaction



C. Martinez, K. Muniz, *Angew. Chem. Int. Ed.* **2015**, *54*, 8287 - 8291.

FULL PAPERS DOI: 10.1002/adsc.201600629 Advanced Synthesis & Catalysis

VIP *Very Important Publication*

Radical Stability as a Guideline in C–H Amination Reactions

Davor Šakić[a] and Hendrik Zipse[b,*]

[a] University of Zagreb, Faculty of Pharmacy and Biochemistry, Ante Kovačića 1, 10000 Zagreb, Croatia
[b] Department of Chemistry, LMU Muenchen, Butenandtstrasse 5–13, 81377 Muenchen, Germany
Fax: (+49)-89-2180-77738; phone: (+49)-89-2180-77737; e-mail: zipse@cup.uni-muenchen.de

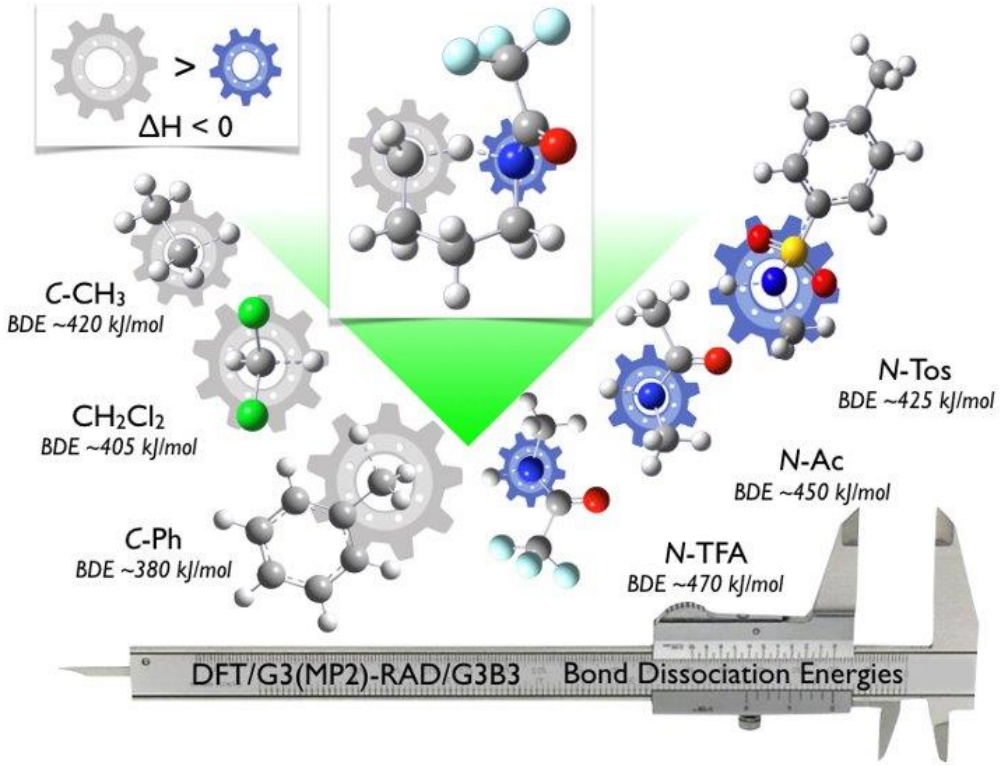
$$\underset{\mathbf{1}}{\dot{C}H_3} + \underset{C_x-H}{H\text{-}CR_3} \rightarrow \underset{1H}{CH_4} + \underset{\mathbf{C}_x}{\dot{C}R_3} \qquad RSE(\mathbf{C}_x) = \Delta H_{rx,298} \qquad (1)$$

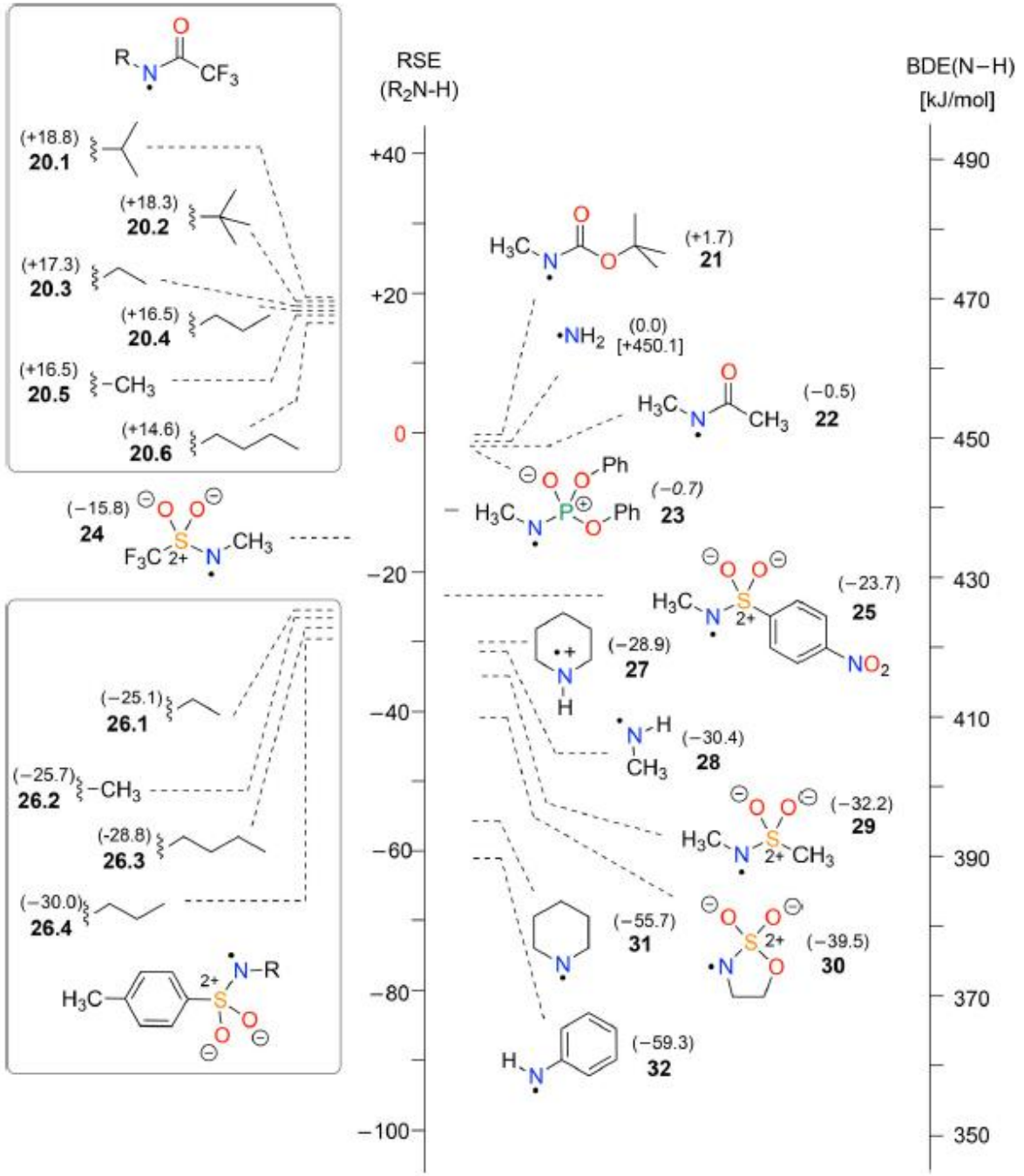
$$\underset{\mathbf{15}}{\dot{N}H_2} + \underset{N_x-H}{H\text{-}NR_2} \rightarrow \underset{15H}{NH_3} + \underset{\mathbf{N}_x}{\dot{N}R_2} \qquad RSE(\mathbf{N}_x) = \Delta H_{rx,298} \qquad (2)$$

$$BDE(\mathbf{C}_{xx}\text{–}\mathbf{H}) = BDE(\mathbf{1H/1}) + RSE(\mathbf{C}_x) \qquad (3)$$

$$BDE(\mathbf{N}_x\text{–}\mathbf{H}) = BDE(\mathbf{15H/15}) + RSE(\mathbf{N}_x) \qquad (4)$$

$$\Delta H^{\ddagger}_{298} = E_0 + \alpha \Delta H_{rxn,298} \qquad (5)$$

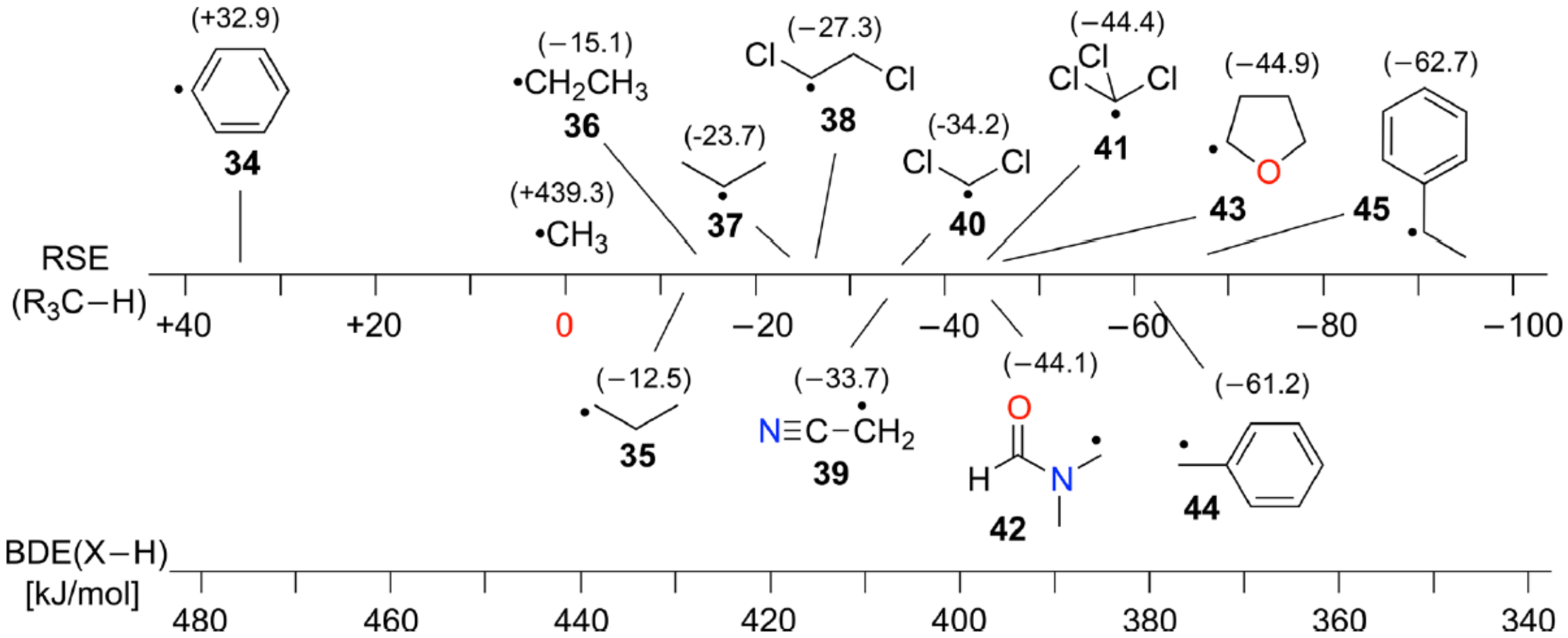




Šakić, D. and Zipse, H., *Adv. Synth. Catal.*, **2016**, *358*, 3983–3991.

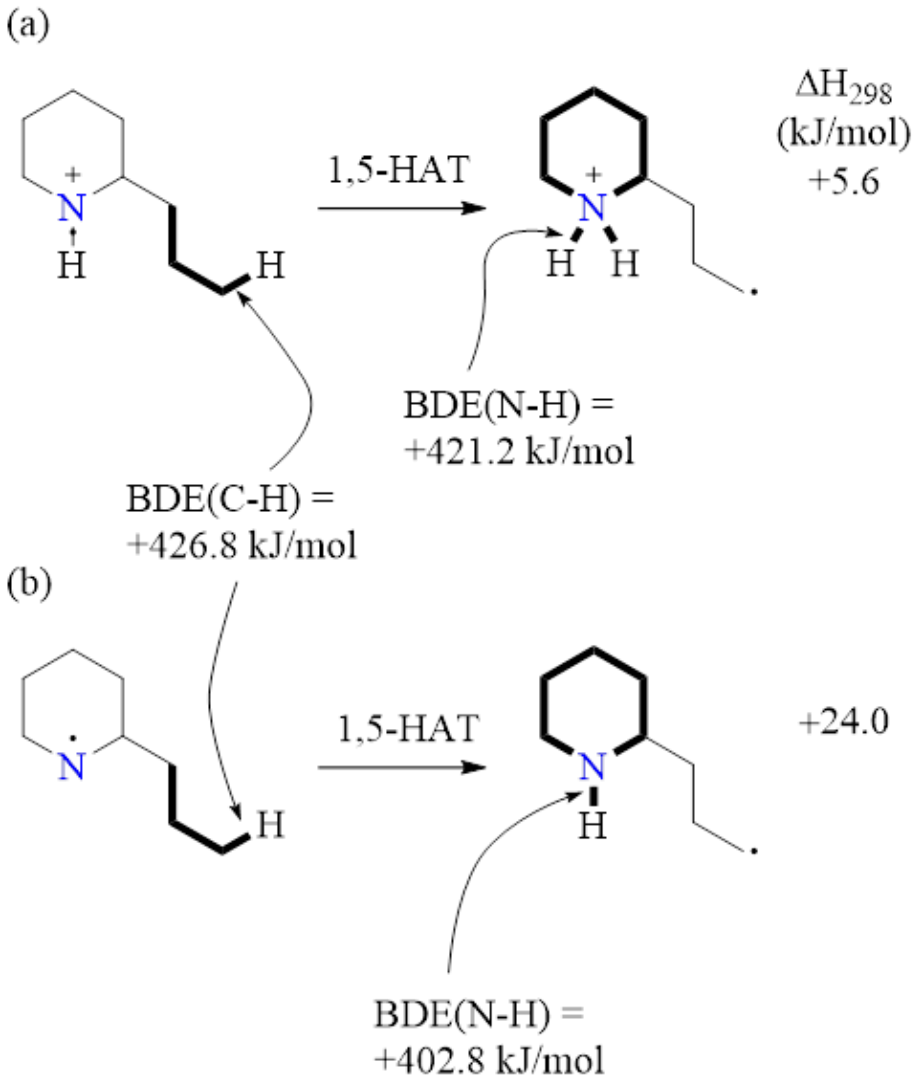
Radical stabilization energies (RSE) and bond dissociation energies (BDE) for aminyl radicals

RSE and BDE values for selected *C*-centred radicals



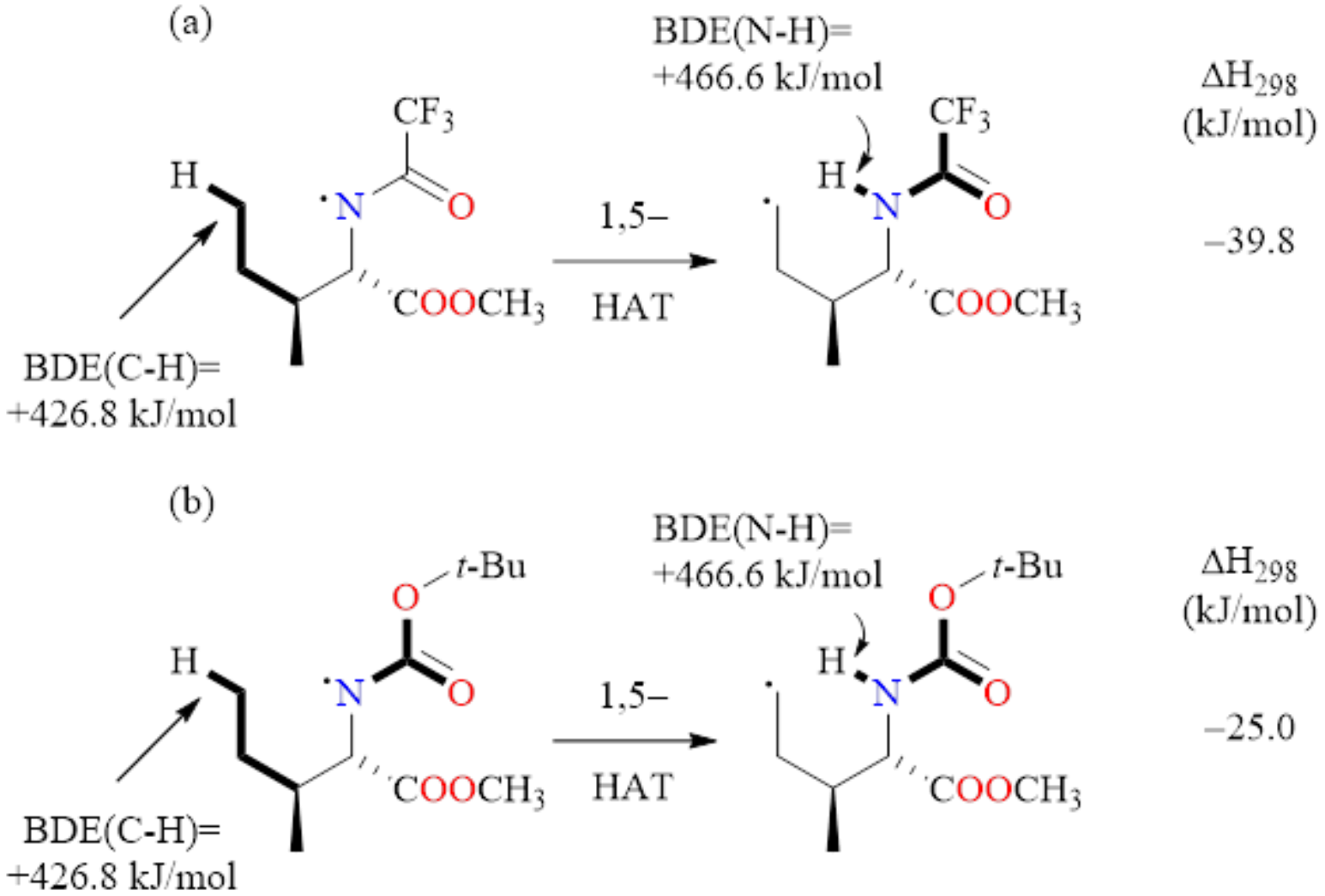
Šakić, D. and Zipse, H., *Adv. Synth. Catal.*, **2016**, *358*, 3983–3991.

The effect of reaction medium on the thermochemical profile of the HAT step for the classical HLF reaction scheme



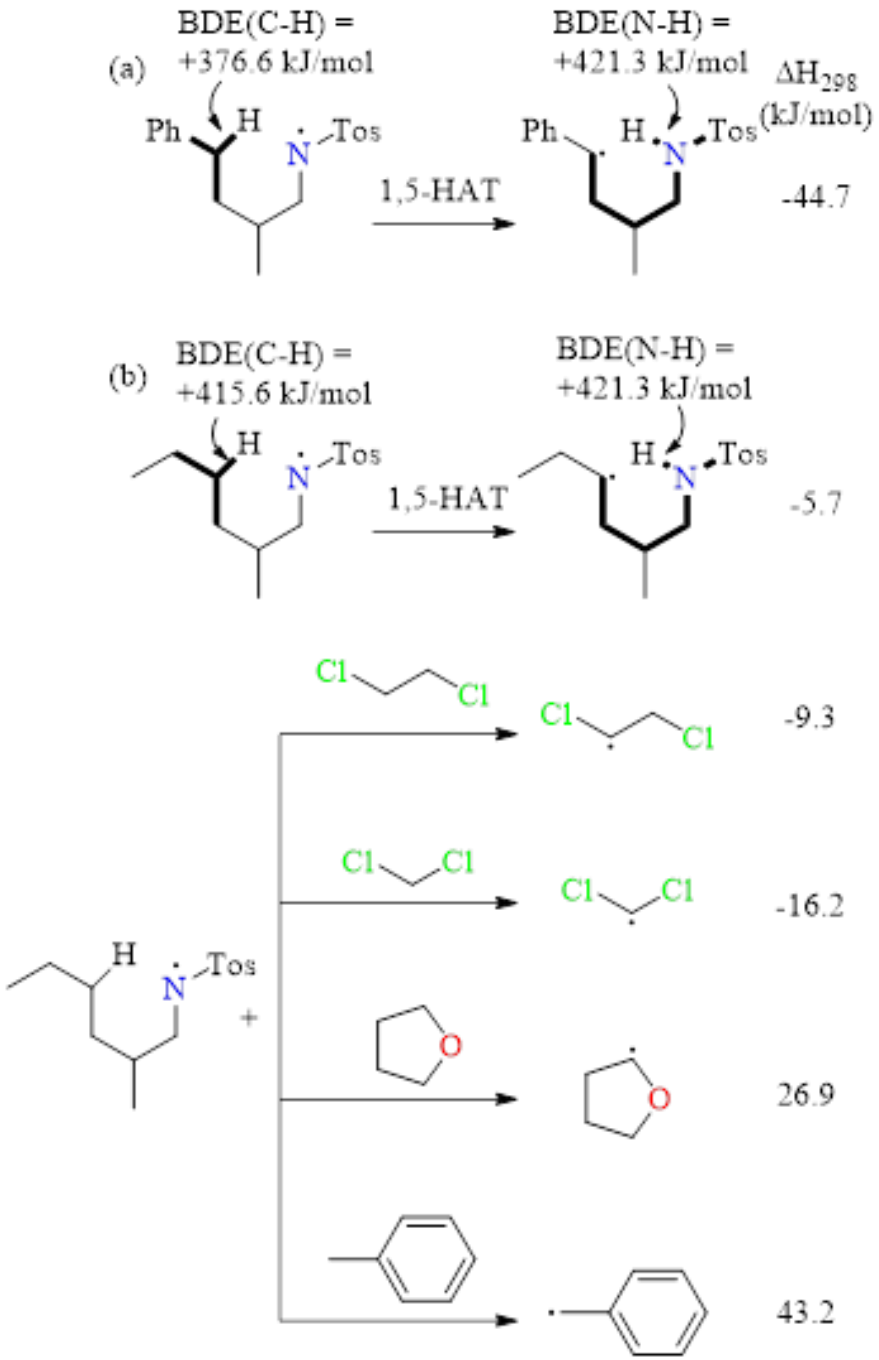
Šakić, D. and Zipse, H., *Adv. Synth. Catal.*, **2016**, *358*, 3983–3991.

Thermochemical profile of 1,5-HAT step for the "Corey modification"



Šakić, D. and Zipse, H., *Adv. Synth. Catal.*, **2016**, *358*, 3983–3991.

Thermochemical profile of 1,5-HAT step within the "Suarez modification" and intermolecular HAT involving solvent molecules



Šakić, D. and Zipse, H., *Adv. Synth. Catal.*, **2016**, *358*, 3983–3991.

Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

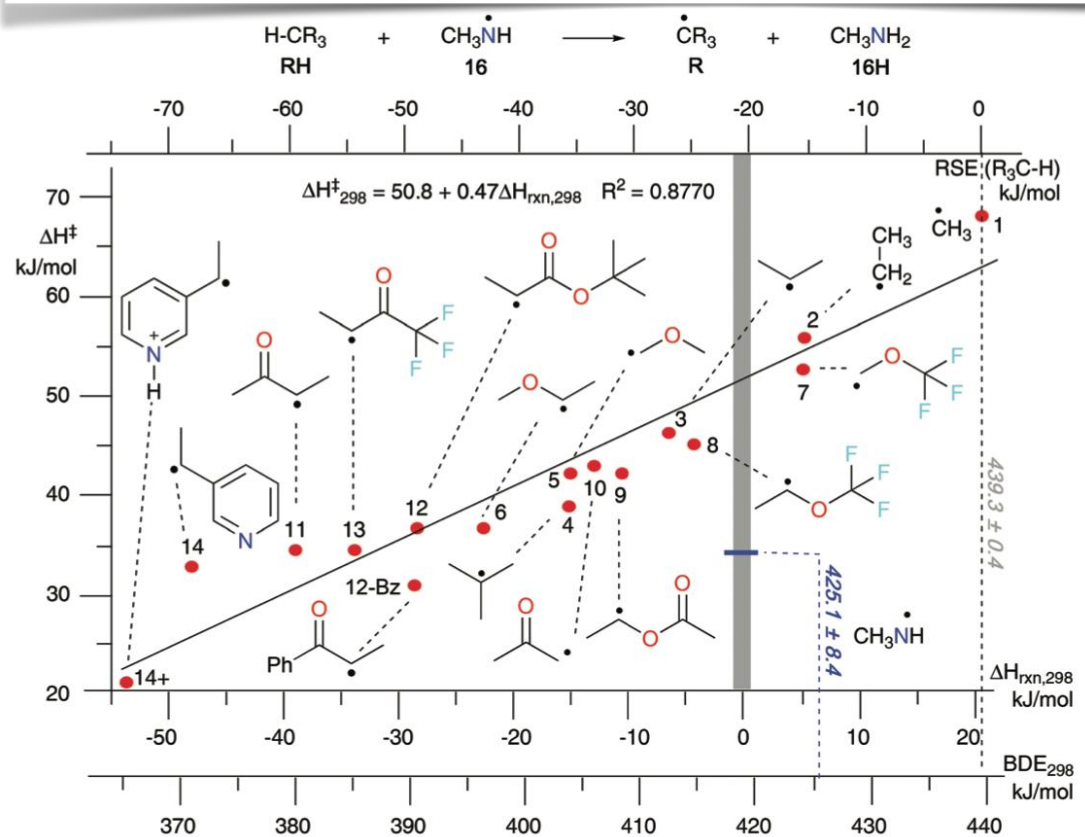
PAPER

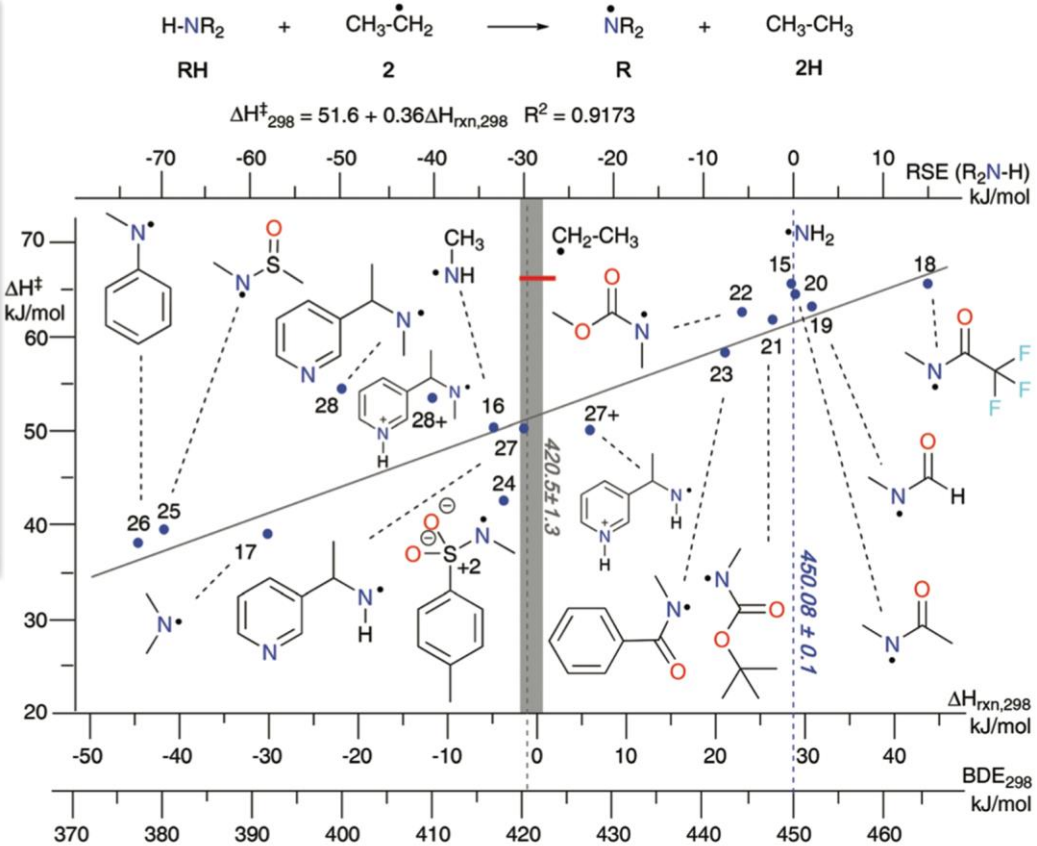
Check for updates

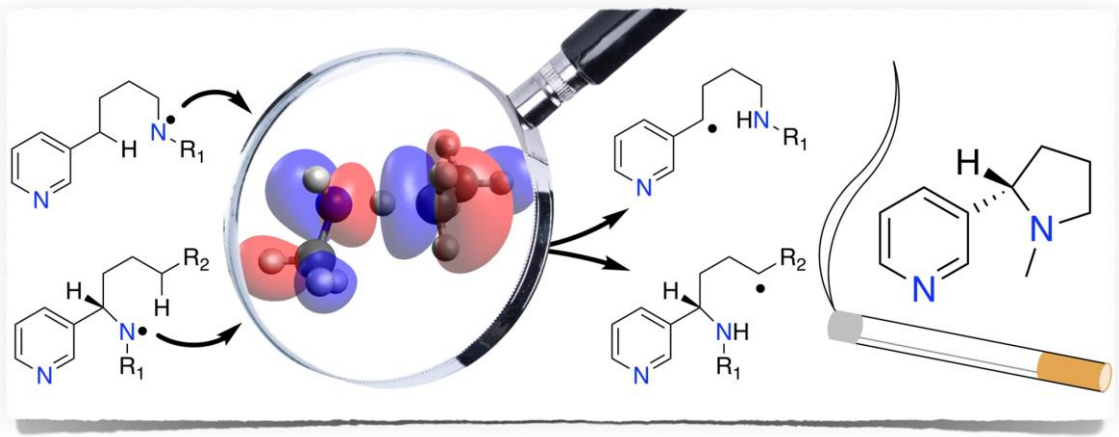
Cite this: *Org. Biomol. Chem.*, 2021, **19**, 854

Role of substituents in the Hofmann–Löffler–Freytag reaction. A quantum-chemical case study on nicotine synthesis†‡

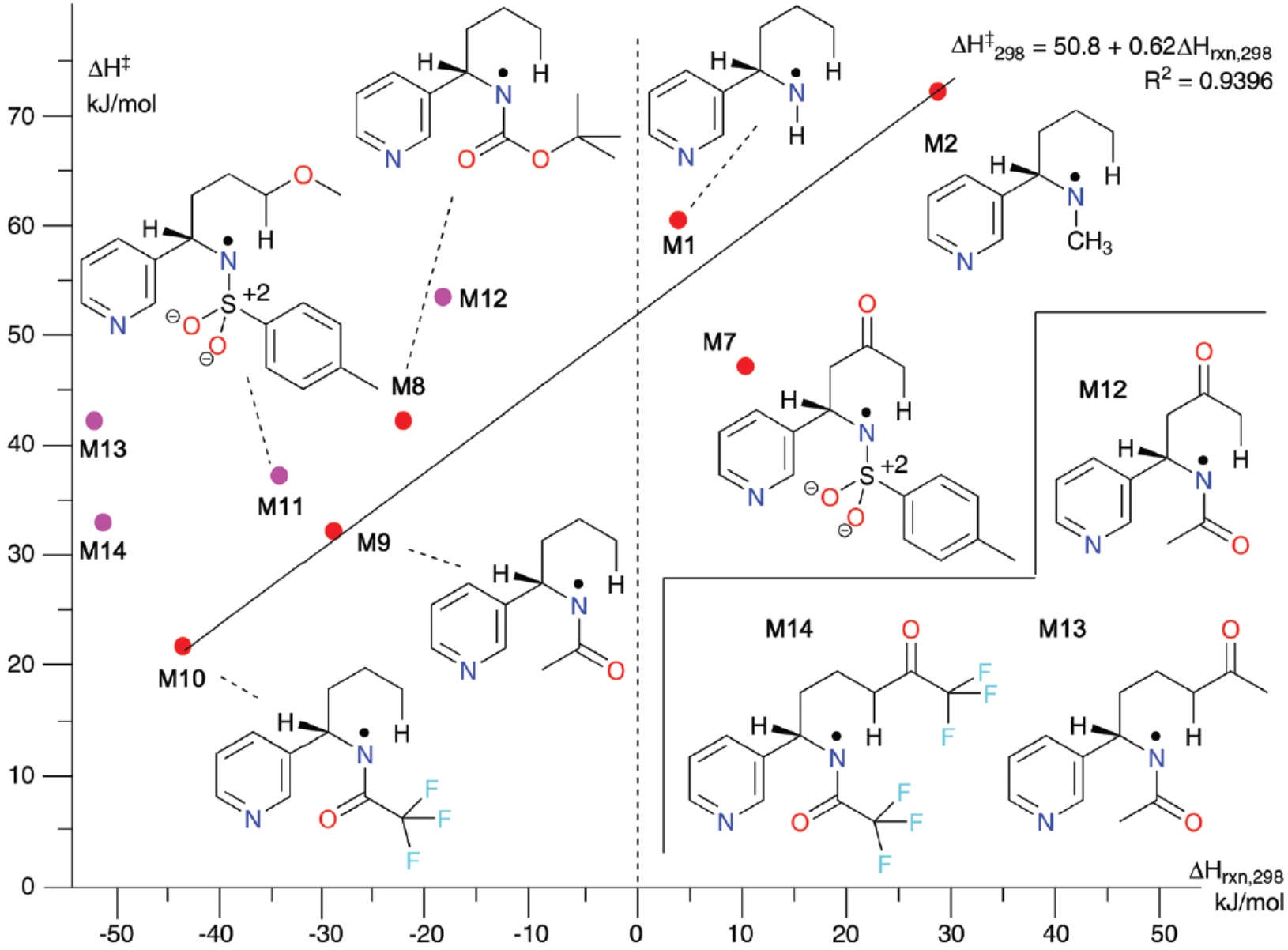
Sofia Shkunnikova,[a] Hendrik Zipse [b] and Davor Šakić *[a]







Application of Bell-Evans-Polany principle



S. Shkunnikova, H. Zipse, D. Šakić, *Org. Biomol. Chem.* **2021**, *19*, 854–865.

Summary

- Calculations have been done with a goal to elucidate the parameters guiding the HLF reaction.
- However, much work is left to be done!
- A switch that accounts for 1,5 or 1,6-HAT regioselectivity is to be determined.
- The role of the oxidant in the shift from inter- to intramolecular HAT steps has to be quantified.
- A switch between ionic and radical pathways is to be established.

Thank you for you attention!

HRZZ project UIP-2020-02-4857