LIGHT⚡RING & SUPEK

kako napredno računanje omogućava rasvjetljavanje reakcija pregrađivanja

#SrceDEI2024

doc. dr. sc. Davor Šakić

Sveučilište u Zagrebu
Farmaceutsko-biokemijski fakultet

HrZZ
Croatian Science
Foundation

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Light-Driven Functionalization of Unreactive Sites Using Oxidative Animation LIGHT-N-RING

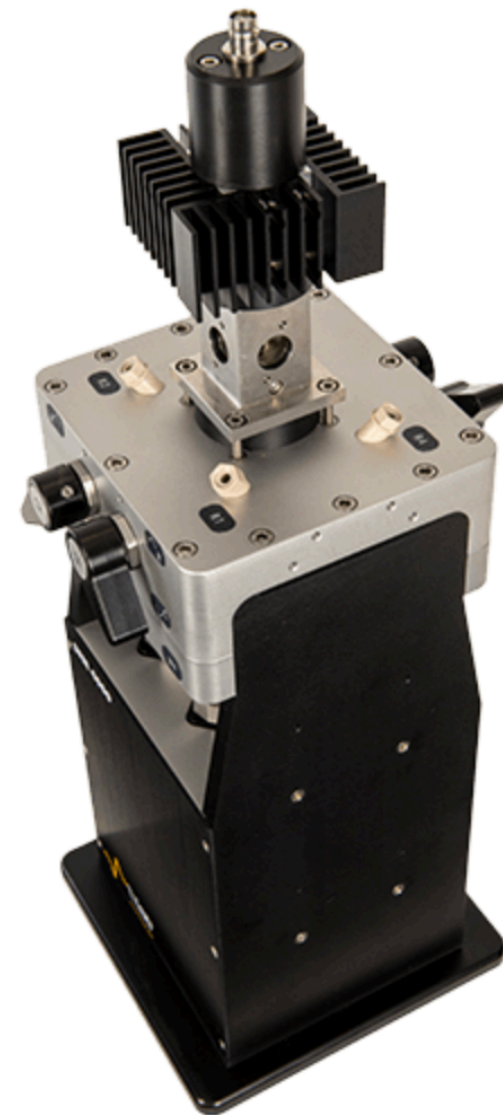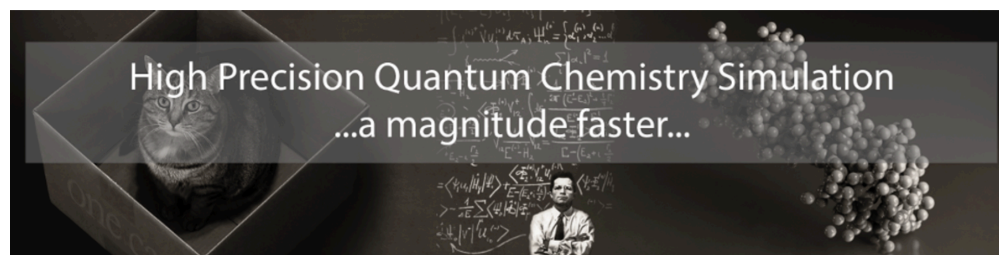| Funded by:	Supported by:	Project details
HRZZ Croatian Science Foundation		doc. dr. sc. Davor Šakić
		HRZZ project UIP-2020-02-4857
		February 1, 2021 – January 31, 2026
		Project budget: 2 000 000,00 kn
		Location: University of Zagreb,
		Faculty of Pharmacy and Biochemistry

Photochemistry in the past
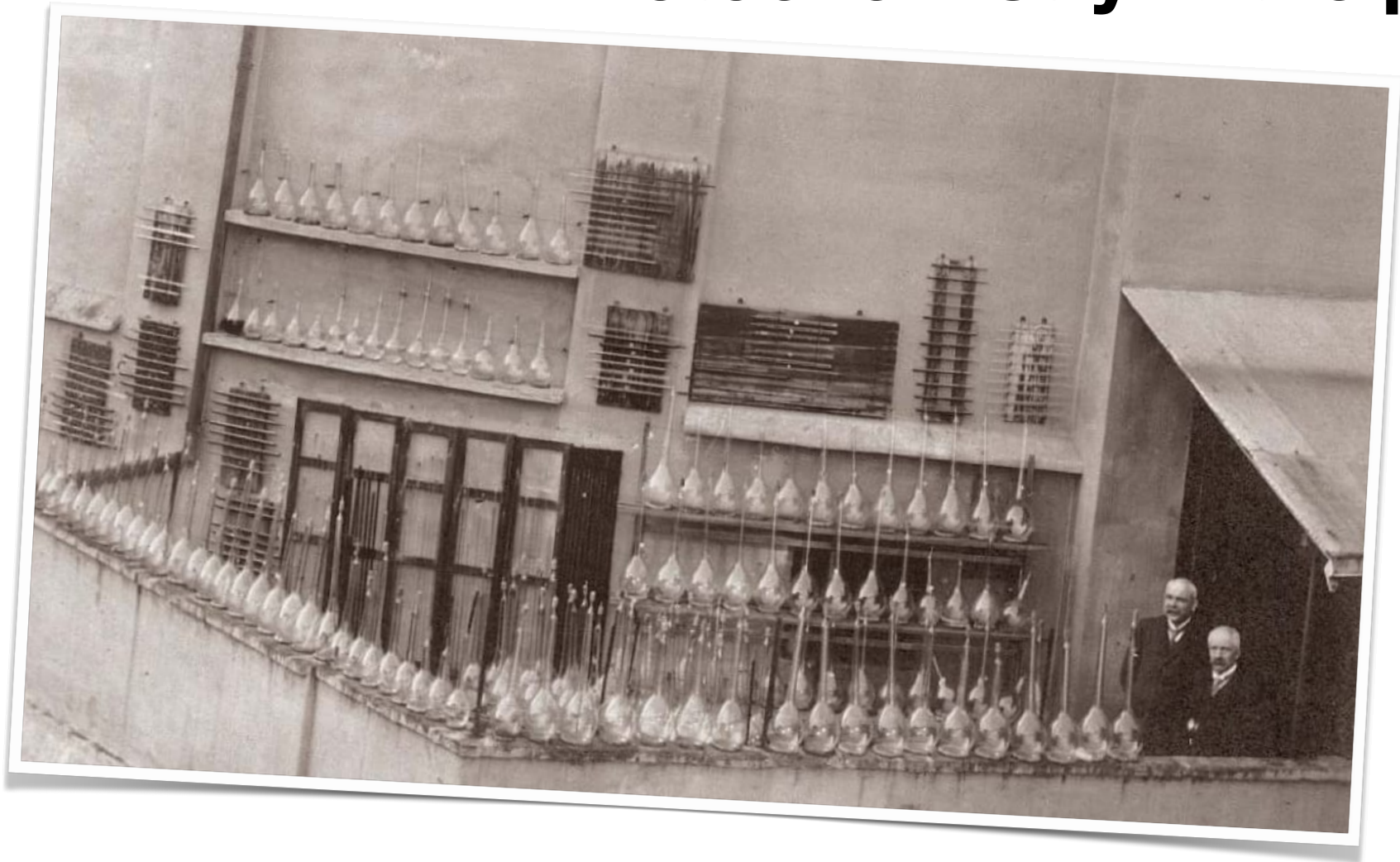
Research

Equipment:

Research
Programs & workstations:

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Chemistry at the speed of graphics...

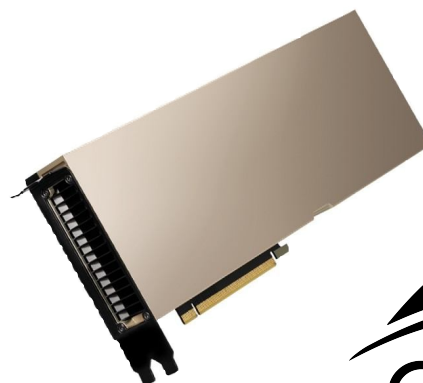| Home | Products | Performance | Accuracy | Pricing | Publications | Demo | Store | About | News |

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H₂SO₄

I) Nitrogen activation

1. H₂SO₄
2. 140°C

base

II) Radical generation

Δ

III) 1,5-HAT transfer

IV) Radical termination
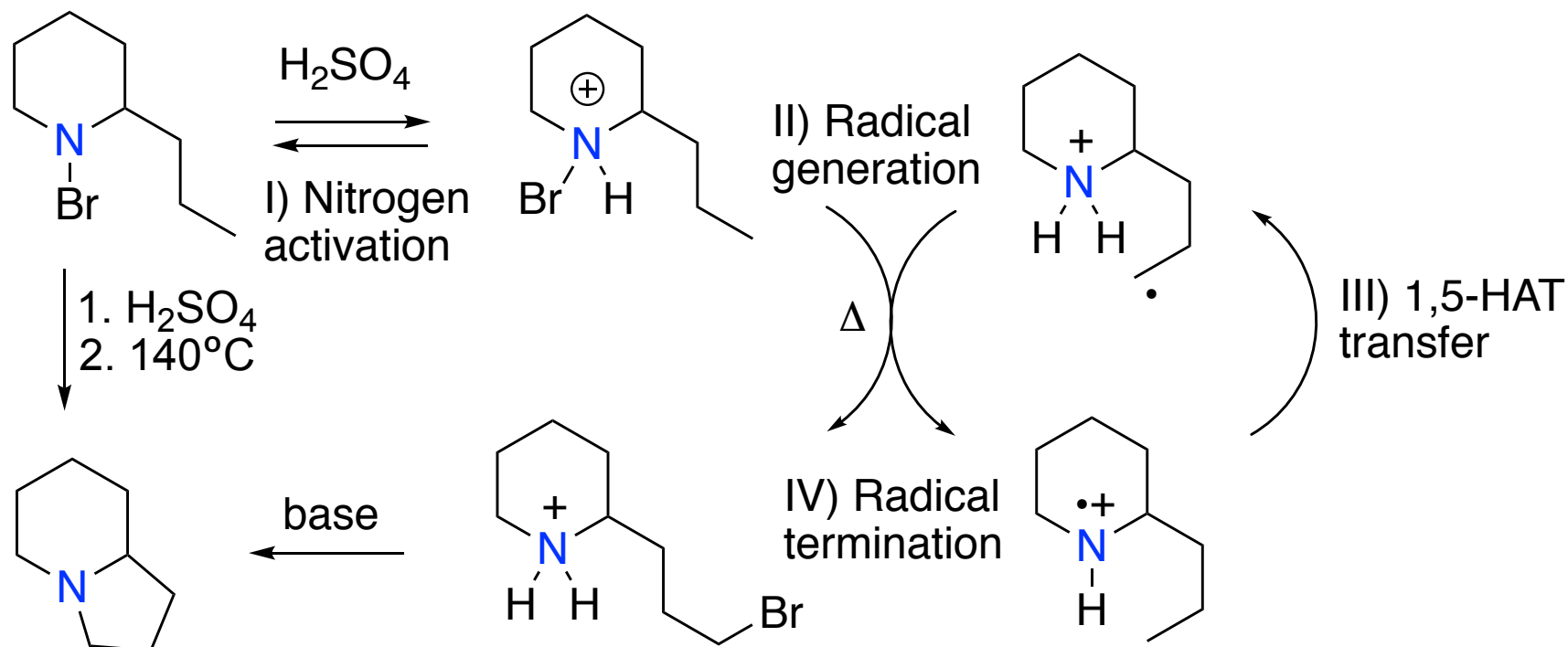
Photoinduced Remote Functionalization of Amides and Amines Using Electrophilic Nitrogen Radicals

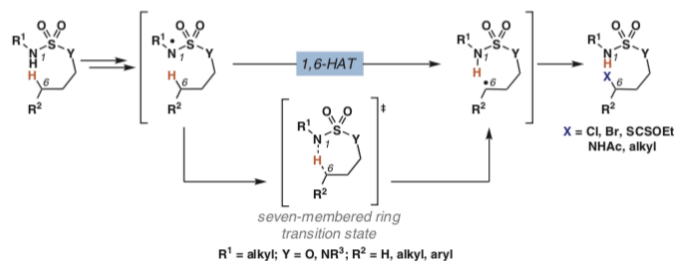Sara P. Morcillo[+], Elizabeth M. Dauncey[+], Ji Hye Kim, James J. Douglas, Nadeem S. Sheikh, and Daniele Leonori*

1,3-Diamine Formation from an Interrupted Hofmann−Löffler Reaction: Iodine Catalyst Turnover through Ritter-Type Amination

Thomas Duhamel,[†,‡] Mario D. Martínez,[†] Ioanna K. Sideri,[†] and Kilian Muñiz*,[†,§]

Modifying Positional Selectivity in C−H Functionalization Reactions with Nitrogen-Centered Radicals: Generalizable Approaches to 1,6-Hydrogen-Atom Transfer Processes

Melanie A. Short
J. Miles Blackburn
Jennifer L. Roizen*

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Durham, NC, 27708-0354, USA
j.roizen@duke.edu

Dedicated to Prof. Brian M. Stoltz as an early celebration of his 50th birthday

seven-membered ring transition state

R[1] = alkyl; Y = O, NR[3]; R[2] = H, alkyl, aryl

1,6-HAT

X = Cl, Br, SCSOEt
NHAc, alkyl

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

Hongwei Zhang[†] and Kilian Muñiz*,[†,‡]

Intramolecular C−H Amination of N-Alkylsulfamides by tert-Butyl Hypoiodite or N-Iodosuccinimide

Kensuke Kiyokawa,*[a] Keisuke Jou,[a] and Satoshi Minakata*[a]

Cooperative Light-Activated Iodine and Photoredox Catalysis for the Amination of C_{sp^3}−H Bonds

Peter Becker, Thomas Duhamel, Christopher J. Stein, Markus Reiher,* and Kilian Muñiz*
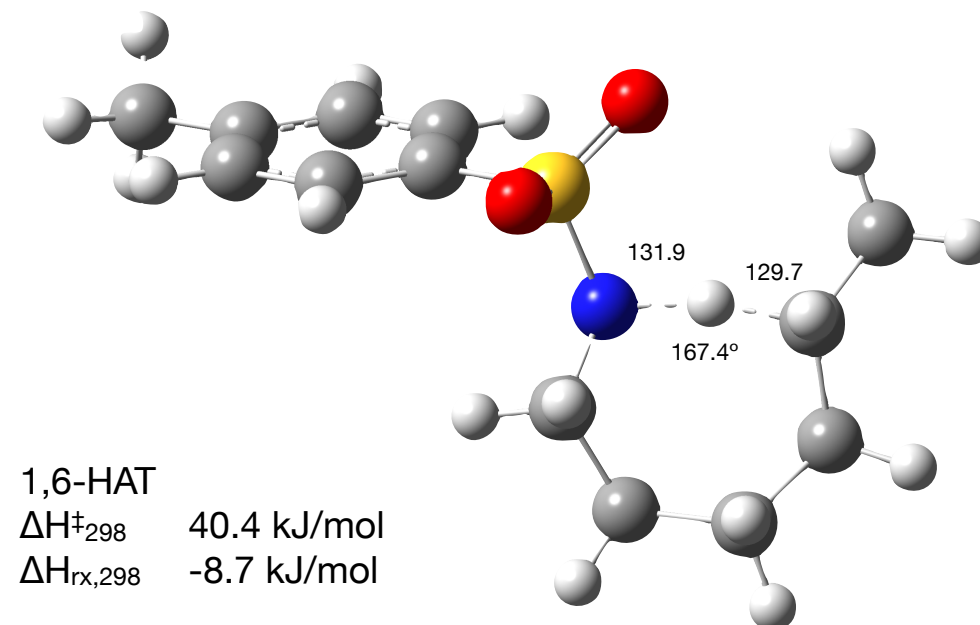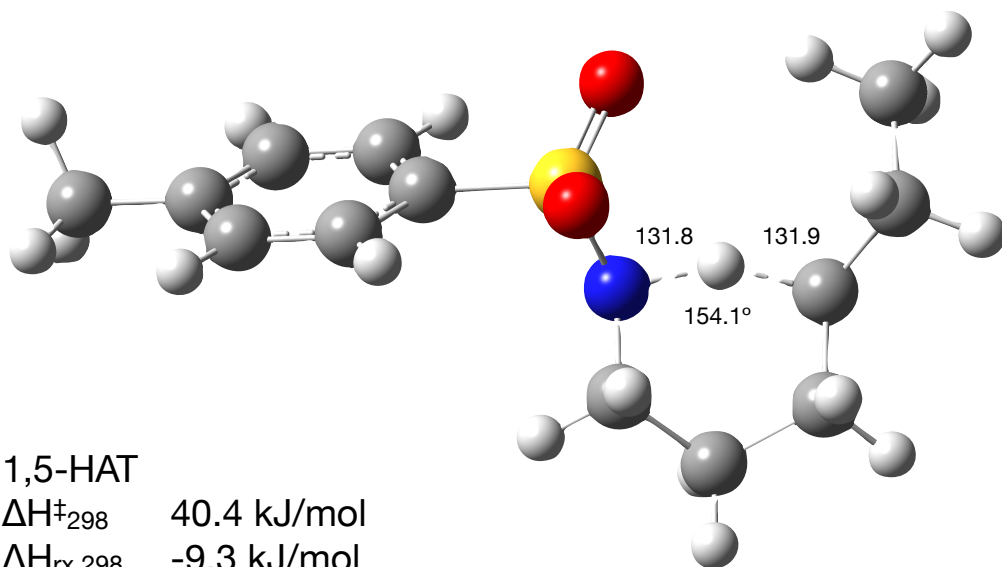
1,4-HAT

1,7-HAT

1,5-HAT

1,6-HAT

inter-HAT

$\Delta H^{\ddagger}_{298}$

angle

G16, H$_{298}$@B3LYP/6-31G(d)

BDE(N-H)
[kJ/mol]

490

RSE
(R$_2$N-H)

(+23.7)   F$_3$C—C(=O)—N(·)—CH$_3$

470

+20

(+3.7)   H$_3$C—C(=O)—N(·)—CH$_3$

450   [+450.1]   ·NH$_2$ 0

(0.0)

[+439.1]   ·CH$_3$ 0
(0.0)

RSE
(R$_3$C-H)

430

(-17.3)   H$_3$C—C$_6$H$_4$—S(=O)$_2$—N(·)—CH$_3$ -20

(-15.4)   H$_2$C(·)—CH$_3$ -20

(-24.4)   H$_3$C—S(=O)$_2$—N(·)—CH$_3$

(-26.2)   H$_3$C—C(·)(H)—CH$_3$

410

(-33.4)   H—N(·)—CH$_3$ -40

(-32.5)   H$_3$C—C(·)(CH$_3$)—CH$_3$ -40

(-57.5)   H$_3$C—N(·)—CH$_3$ -60

390

(-50.7)   H$_2$C(·)—C$_6$H$_5$

-60

370

(-61.5)   H$_3$C—C(·)(H)—C$_6$H$_5$

350

41.0 kJ/mol
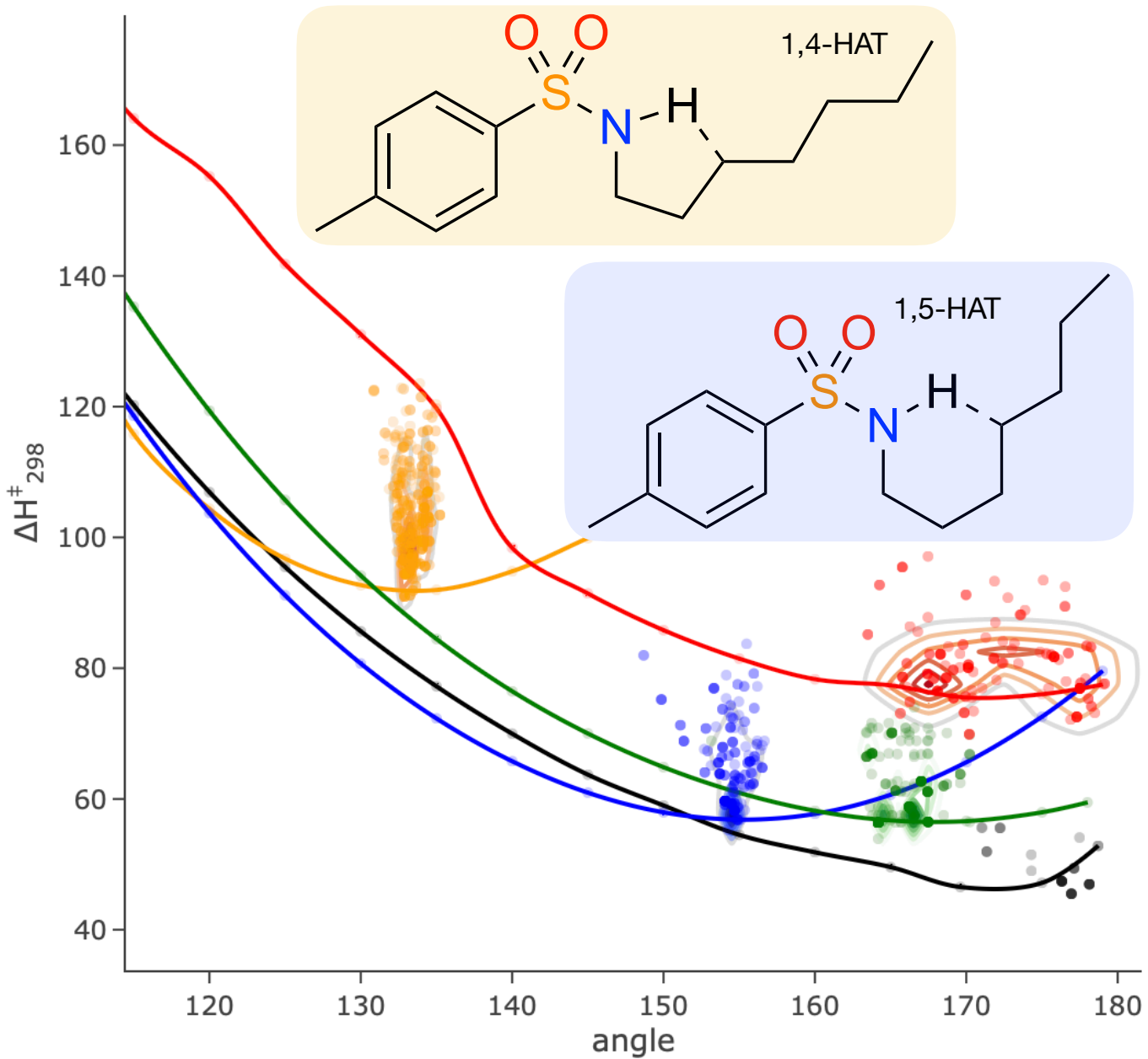
G16, H$_{298}$@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)
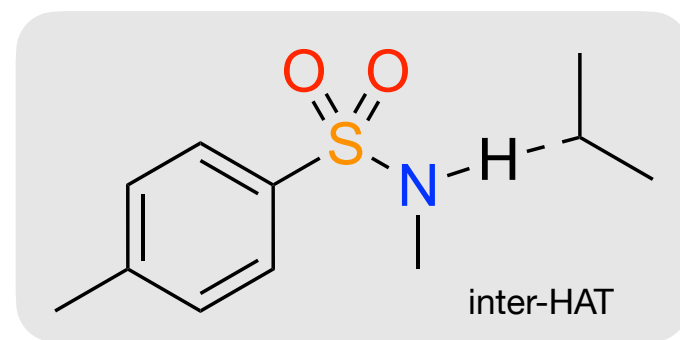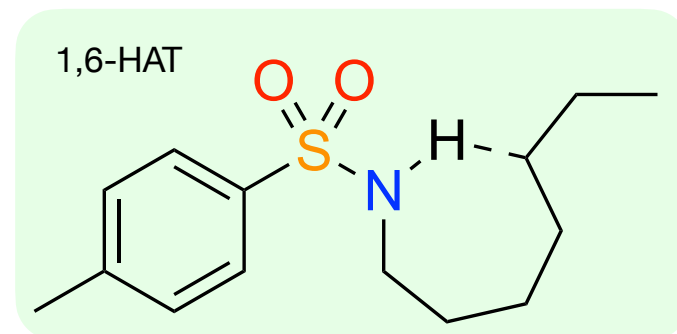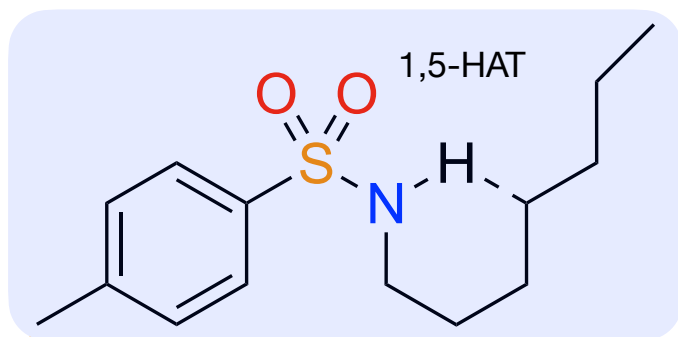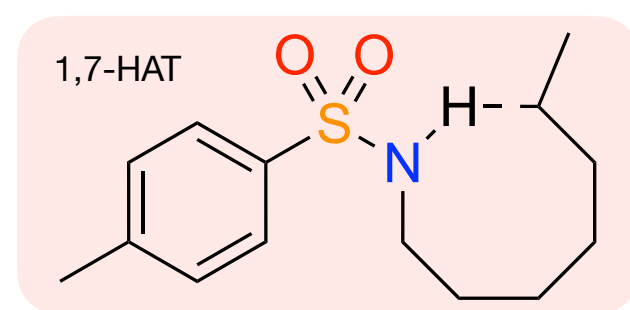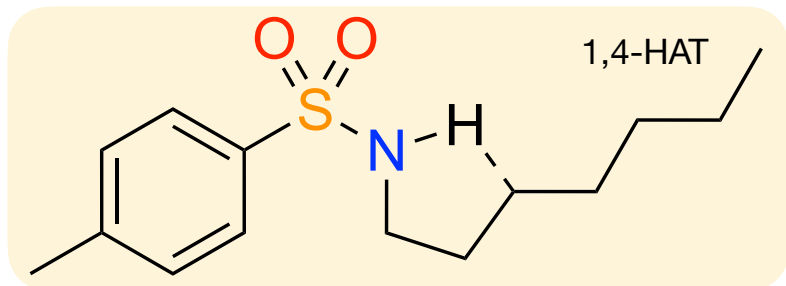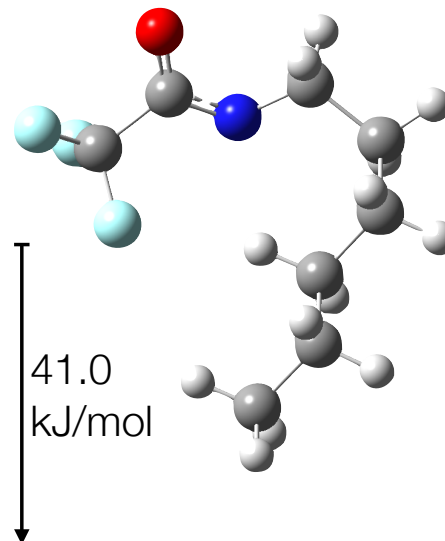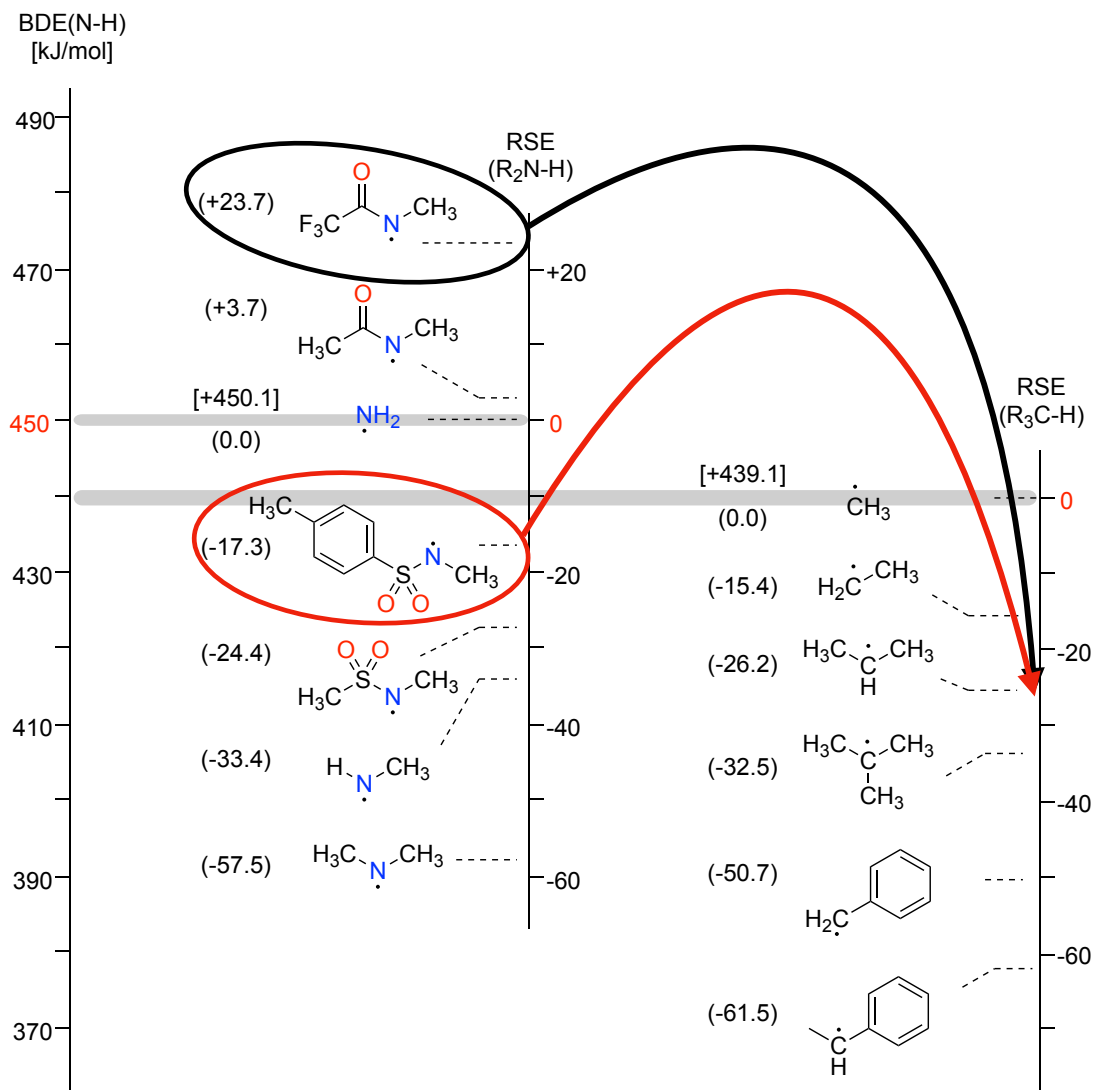
N-triflouroacetyl-hexylamine

	$\Delta H^{\ddagger}_{298}$ kJ/mol	$\Delta H_{rx,298}$ kJ/mol
1,5-HAT	36.6	-37.9
1,6-HAT	38.0	-30.3

N-tosyl-hexylamine

	$\Delta H^{\ddagger}_{298}$ kJ/mol	$\Delta H_{rx,298}$ kJ/mol
1,5-HAT	40.4	-9.3
1,6-HAT	40.4	-8.7

Radical Stability as a Guideline in C–H Amination Reactions

Davor Šakić[a] and Hendrik Zipse[b,*]

BDE(N-H)
[kJ/mol]

490

470

450

430

410

390

370

350

RSE
(R₂N-H)

$+20$

0

-20

-40

-60

(+23.7) F₃C—C(=O)—N(·)—CH₃

(+3.7) H₃C—C(=O)—N(·)—CH₃

[+450.1] ·NH₂

(0.0)

(-17.3) H₃C—(C₆H₄)—S(=O)₂—N(·)—CH₃

(-24.4) H₃C—S(=O)₂—N(·)—CH₃

(-33.4) H—N(·)—CH₃

(-57.5) H₃C—N(·)—CH₃

RSE
(R₃C-H)

0

-20

-40

-60

[+439.1] ·CH₃

(0.0)

(-15.4) H₂C(·)—CH₃

(-26.2) H₃C—C(·)H—CH₃

(-32.5) H₃C—C(·)(CH₃)—CH₃

(-50.7) H₂C(·)—C₆H₅

(-61.5) H₃C—C(·)H—C₆H₅

25.3
kJ/mol

Selective Piperidine Synthesis Exploiting Iodine-Catalyzed C$_{sp}^3$−H Amination under Visible Light

Hongwei Zhang[†] and Kilian Muñiz[*,†,‡]

G16, H₂₉₈@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)
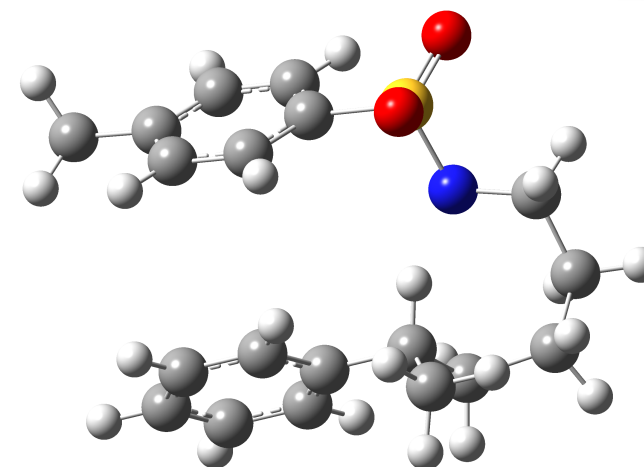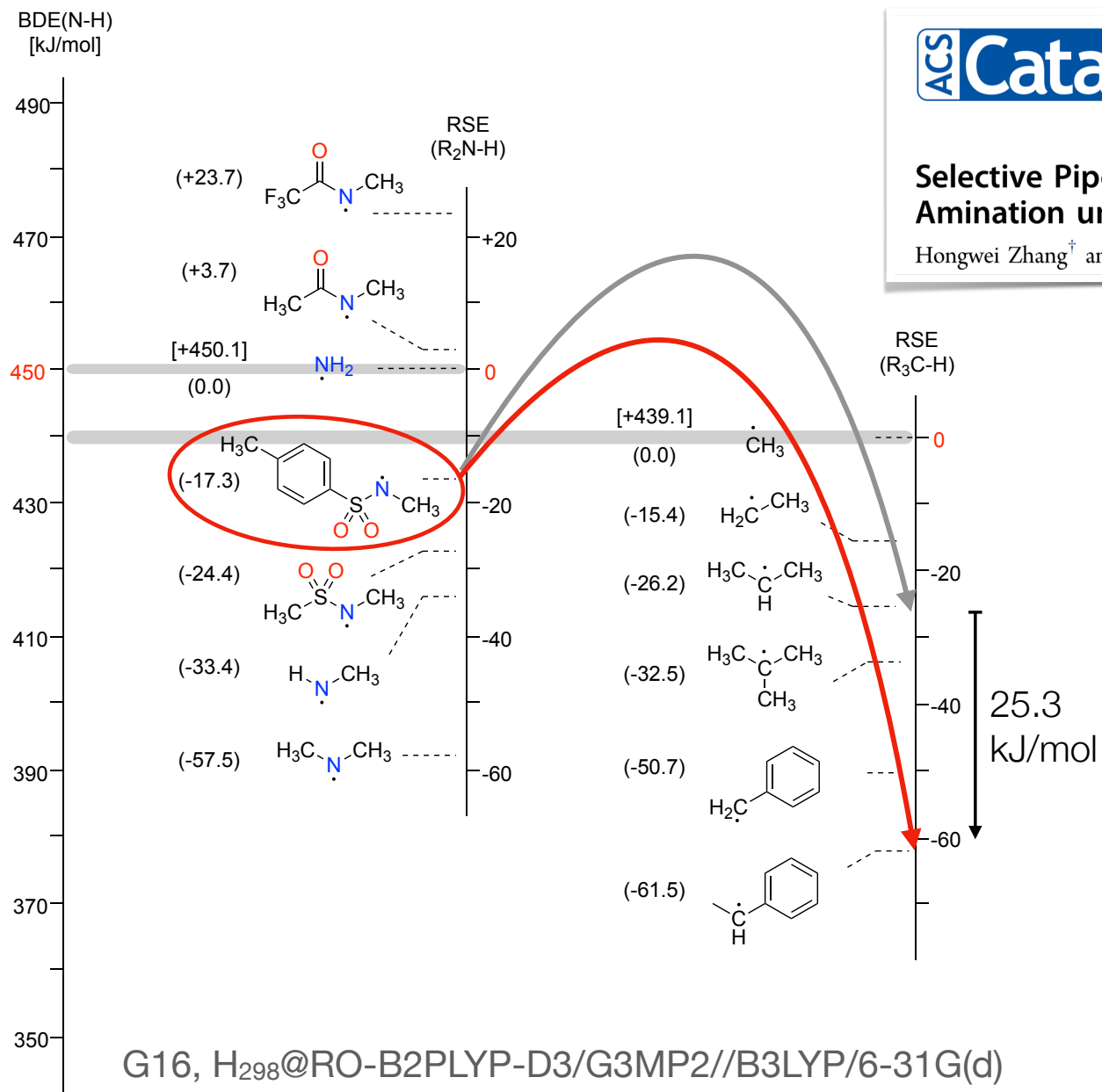
N-tosyl-(5-phenyl)hexylamine		
	$\Delta H^{\ddagger}_{298}$	$\Delta H_{rx,298}$
	kJ/mol	kJ/mol
1,5-HAT	58.9	-13.3
1,6-HAT	40.0	-44.2

No luck…
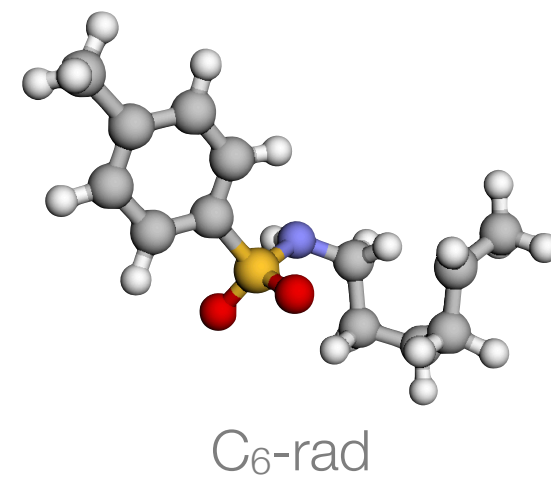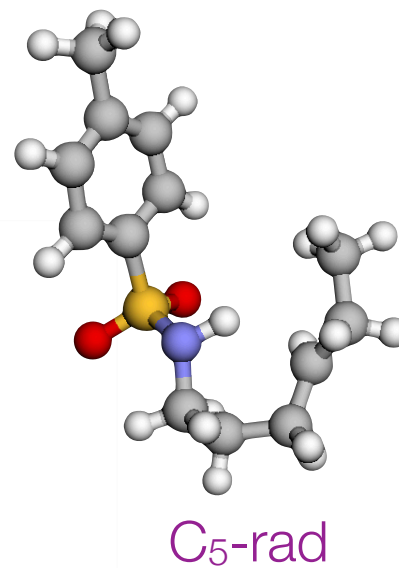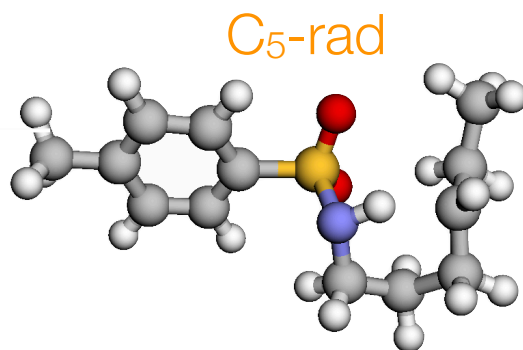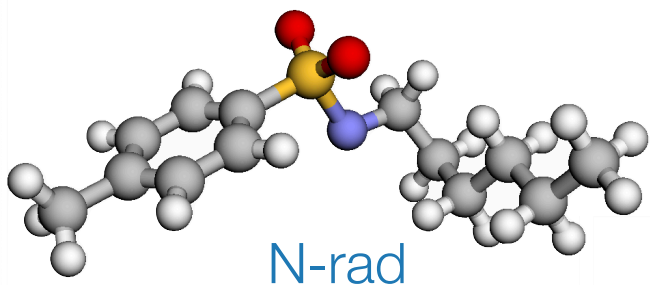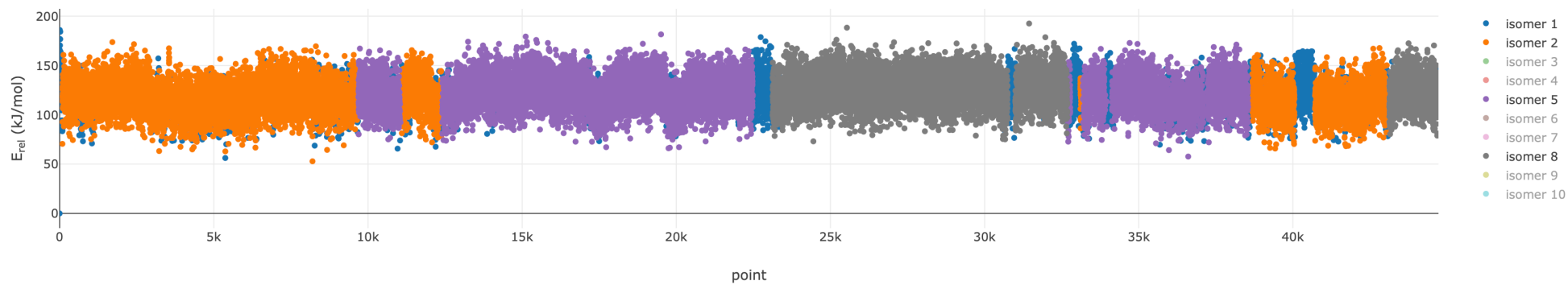
MD

MD@xtb/GFN1, SHAKE=0, HMASS=2, TEMP=298.15K
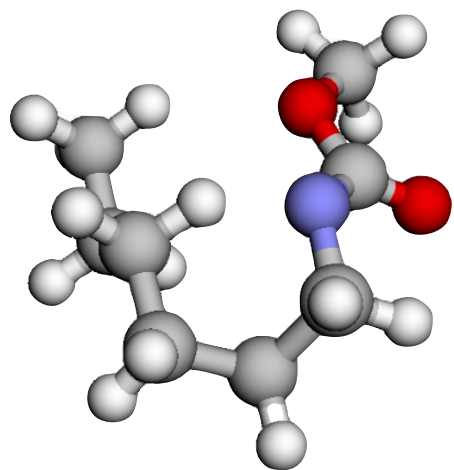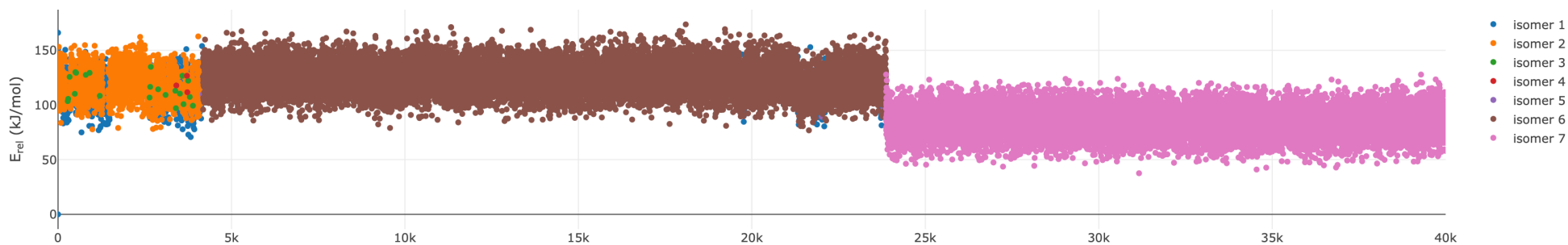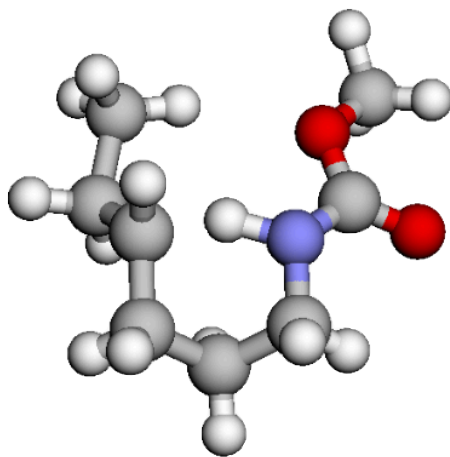
N-rad C$_5$-rad C$_6$-rad C$_2$-rad

BDE(N-H)
[kJ/mol]

490

RSE
(R$_2$N-H)

(+23.7) F$_3$C—C(=O)—N•—CH$_3$

470

+20

(+3.7) H$_3$C—C(=O)—N•—CH$_3$

[+450.1] •NH$_2$

450

0

(0.0)

[+439.1] •CH$_3$

RSE
(R$_3$C-H)

(0.0)

0

H$_3$C—⟨C$_6$H$_4$⟩—S(=O)$_2$—N•—CH$_3$
(-17.3)

-20

(-15.4) H$_2$C•—CH$_3$

430

(-24.4) H$_3$C—S(=O)$_2$—N•—CH$_3$

(-26.2) H$_3$C—C•H—CH$_3$

-20

-40

(-33.4) H—N•—CH$_3$

(-32.5) H$_3$C—C•(—CH$_3$)—CH$_3$

410

-40

(-57.5) H$_3$C—N•—CH$_3$

-60

(-50.7) H$_2$C•—⟨C$_6$H$_5$⟩

390

(-61.5) H$_3$C—C•H—⟨C$_6$H$_5$⟩

-60

370

350

G16, H$_{298}$@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)

BDE(N-H)
[kJ/mol]

490

(+23.7) F_3C—C(=O)—N(•)—CH_3 (O on top)

RSE
(R_2N-H)

470

(+3.7) H_3C—C(=O)—N(•)—CH_3 (O on top)

+20

[+450.1]
450 ——— •NH_2 ——— 0
(0.0)

[+439.1]
(0.0) •CH_3 ——— 0

RSE
(R_3C-H)

RSE
(R_3C-H)

0

(-17.3) H_3C—(ring)—$S(=O)(=O)$—N(•)—CH_3

-20

(-15.4) H_2C(•)—CH_3

(-37.8) H_3C—C(=O)—NH—CH(•)—CH_3 (O on top)

430

(-24.4) H_3C—$S(=O)(=O)$—N(•)—CH_3

-40

(-26.2) H_3C—C(•)(H)—CH_3

-20

(-37.3) H_3C—CH(•)—NH—$S(=O)(=O)$—(ring)—CH_3

410

(-33.4) H—N(•)—CH_3

(-32.5) H_3C—C(•)(CH_3)—CH_3

-40

(-41.2) H_3C—CH(•)—NH—$S(=O)(=O)$—CH_3

390

(-57.5) H_3C—N(•)—CH_3

-60

(-50.7) H_2C(•)—(ring)

-60

(-47.7) F_3C—C(=O)—NH—CH(•)—CH_3 (O on top)

370

(-61.5) (ring)—CH(•)—CH_3 (with H below)

(-50.8) (ring)—C(=O)—NH—CH(•)—CH_3 (O on top)

(-51.5) H_3C—NH—CH_2(•)

350

(-58.2) H_3C—NH—CH(•)—CH_3

G16, H_{298}@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)

BDE(N-H) [kJ/mol]

490 —

(+23.7) F_3C—C(=O)—N($\cdot$)—CH_3

RSE (R₂N-H)

470 —

(+3.7) H_3C—C(=O)—N($\cdot$)—CH_3

+20

+20

450 — (+450.1) · NH_2 0

(0.0)

RSE (R₃C-H)   RSE (R₃C-H)

[+439.1] · CH_3 0   0

(0.0)

(-17.3) H_3C—⬡—S(=O)(=O)—N($\cdot$)—CH_3 -20

430 —

(-15.4) $H_2\dot{C}$—CH_3

(-24.4) H_3C—S(=O)(=O)—N($\cdot$)—CH_3 -20

-20

(-26.2) H_3C—$\dot{C}$(H)—CH_3

-40

(-33.4) H—N($\cdot$)—CH_3

(-32.5) H_3C—$\dot{C}$(CH_3)—CH_3

410 —

(-37.8) H_3C—C(=O)—N(H)—$\dot{C}$(H)—CH_3

(-37.3) H_3C—$\dot{C}$(H)—N(H)—S(=O)(=O)—⬡—CH_3

(-57.5) H_3C—N($\cdot$)—CH_3 -60

(-50.7) $H_2\dot{C}$—⬡

-40

390 —

(-41.2) H_3C—$\dot{C}$(H)—N(H)—S(=O)(=O)—CH_3

-60

(-47.7) F_3C—C(=O)—N(H)—$\dot{C}$(H)—CH_3

(-61.5) $\dot{C}$(H)(⬡)—CH_3

370 —

(-50.8) ⬡—C(=O)—N(H)—$\dot{C}$(H)—CH_3

(-51.5) H_3C—N(H)—$\dot{C}H_2$

350 —

(-58.2) H_3C—N(H)—$\dot{C}$(H)—CH_3

G16, H₂₉₈@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)

N-tosyl-hexylamine

	$\Delta H^{\ddagger}_{298}$ kJ/mol	$\Delta H_{rx,298}$ kJ/mol
1,5-HAT_{NC}	40.4	-9.3
1,6-HAT_{NC}	40.4	-8.7
1,5-HAT_{CC}	57.4	-22.5
1,2-HAT_{NC}	153.2	-20.3
1,4-HAT_{CC}	111.2	-21.9

134.7   138.0   153.2°

BDE(N-H)
[kJ/mol]

490

**Selective Piperidine Synthesis Exploiting Iodine-Catalyzed C$_{sp}^3$−H Amination under Visible Light**

Hongwei Zhang[†] and Kilian Muñiz*[†,‡]

RSE
(R$_2$N-H)

470

(+23.7) F$_3$C—C(=O)—N•—CH$_3$

+20

(+3.7) H$_3$C—C(=O)—N•—CH$_3$

450

[+450.1] •NH$_2$ 0

(0.0)

RSE
(R$_3$C-H)

RSE
(R$_3$C-H)

[+439.1]   0   0

(0.0) •CH$_3$

(-17.3) H$_3$C—C$_6$H$_4$—S(=O)$_2$—N•—CH$_3$ -20

(-15.4) •H$_2$C—CH$_3$

(-24.4) H$_3$C—S(=O)$_2$—N•—CH$_3$

-40

(-26.2) H$_3$C—•C(H)—CH$_3$ -20   -20

(-33.4) H—N•—CH$_3$

(-32.5) H$_3$C—•C(CH$_3$)—CH$_3$

430

410

(-37.8) H$_3$C—C(=O)—NH—•C(H)—CH$_3$

(-37.3) H$_3$C—•C(H)—NH—S(=O)$_2$—C$_6$H$_4$—CH$_3$

(-57.5) H$_3$C—N•—CH$_3$

-60

(-50.7) H$_2$C•—C$_6$H$_5$

-40   -40

(-41.2) H$_3$C—•C(H)—NH—S(=O)$_2$—CH$_3$

(-47.7) F$_3$C—C(=O)—NH—•C(H)—CH$_3$

(-61.5) H$_3$C—•C(H)—C$_6$H$_5$ -60   -60

390

(-50.8) C$_6$H$_5$—C(=O)—NH—•C(H)—CH$_3$

(-51.5) H$_3$C—NH—•CH$_2$

370

(-58.2) H$_3$C—NH—•C(H)—CH$_3$

350

G16, H$_{298}$@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)

BDE(N-H) [kJ/mol]

RSE (R₂N-H)

490

470 — (+23.7) F_3C—C(=O)—N(·)—CH_3

(+3.7) H_3C—C(=O)—N(·)—CH_3

450 — [+450.1] $\overset{\cdot}{N}H_2$ — 0

(0.0)

(-17.3) H_3C—C₆H₄—S(=O)₂—N(·)—CH_3

430 — -20

(-24.4) H_3C—S(=O)₂—N(·)—CH_3

410 — -40

(-33.4) H—N(·)—CH_3

(-57.5) H_3C—N(·)—CH_3

390 — -60

370

350

G16, H₂₉₈@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)

RSE (R₃C-H)

[+439.1] $\overset{\cdot}{C}H_3$ — 0

(0.0)

(-15.4) $H_2\overset{\cdot}{C}$—CH_3

(-26.2) H_3C—$\overset{\cdot}{C}H$—CH_3

(-32.5) H_3C—$\overset{\cdot}{C}$(CH_3)—CH_3

(-50.7) $H_2\overset{\cdot}{C}$—C₆H₅

(-61.5) $\overset{\cdot}{C}H$(C₆H₅)—CH_3(H)

-20

-40

-60

RSE (R₃C-H)

0

-20

-40

-60

(-37.8) H_3C—C(=O)—NH—$\overset{\cdot}{C}H$—CH_3

(-37.3) H_3C—$\overset{\cdot}{C}H$—NH—S(=O)₂—C₆H₄—CH_3

(-41.2) H_3C—$\overset{\cdot}{C}H$—NH—S(=O)₂—CH_3

(-47.7) F_3C—C(=O)—NH—$\overset{\cdot}{C}H$—CH_3

(-50.8) C₆H₅—C(=O)—NH—$\overset{\cdot}{C}H$—CH_3

(-51.5) H_3C—NH—$\overset{\cdot}{C}H_2$

(-58.2) H_3C—NH—$\overset{\cdot}{C}H$—CH_3

23.7 kJ/mol

ACS Catalysis — Letter — pubs.acs.org/acscatalysis

Selective Piperidine Synthesis Exploiting Iodine-Catalyzed C$_{sp}^3$–H Amination under Visible Light

Hongwei Zhang[†] and Kilian Muñiz*[†,‡]

N-tosyl-(5-phenyl)hexylamine

	$\Delta H^{\ddagger}_{298}$ kJ/mol	$\Delta H_{rx,298}$ kJ/mol
1,5-HAT$_{NC}$	58.9	-13.3
1,6-HAT$_{NC}$	40.0	-44.2
1,5-HAT$_{CC}$	88.1	25.0

Article

Regioselective Rearrangement of Nitrogen- and Carbon-Centered Radical Intermediates in the Hofmann–Löffler–Freytag Reaction

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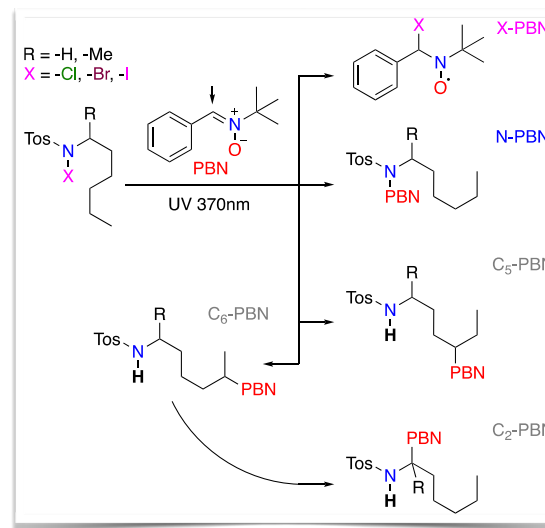
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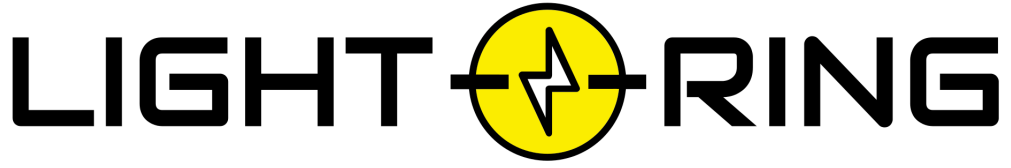
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