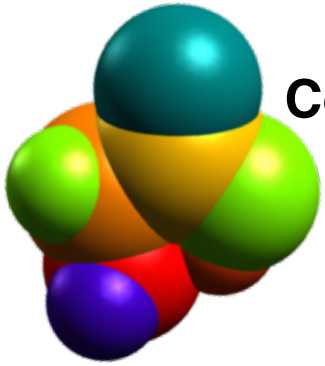


Computational
Chemistry
Day 2022

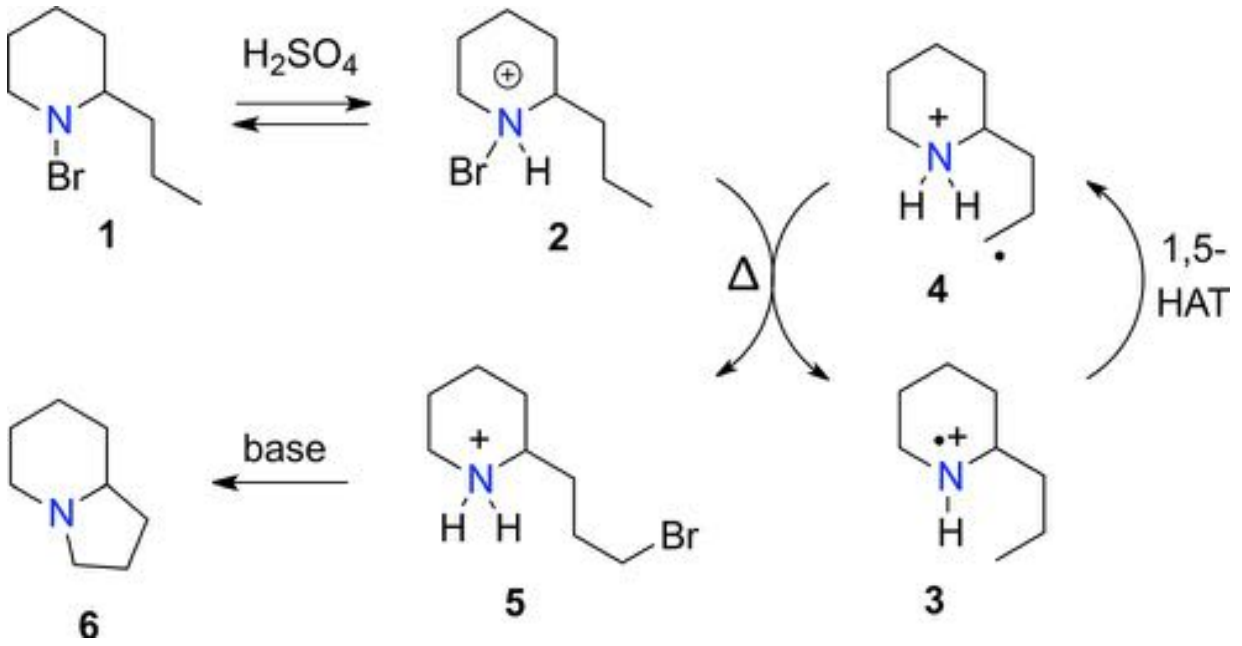
Shining Light on the Old Reaction; Renaissance of the Hofmann-Löffler-Freytag reaction

doc. dr. sc. Davor Šakić

LIGHT-RING

HrZZ
Croatian Science
Foundation

Hofmann



558

106. A. W. Hofmann: Ueber die Einwirkung des Broms in alkalischer Lösung auf die Amine.

[Aus dem Berl. Univ.-Laborat. No. DXVII.]

(Vorgetragen vom Verfasser.)

1881.

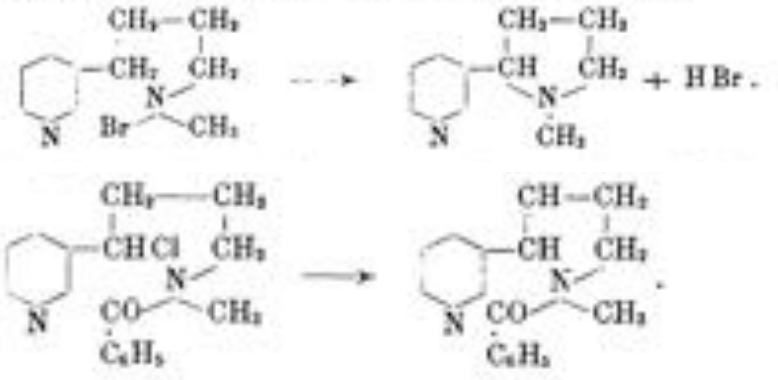
Löffler, Kober, Freytag

503. Karl Löffler und Samy Kober:
Über die Bildung des *i*-Nicotins aus *N*-Methyl-γ-pyridyl-butylamin (Dihydrometanicotin).

[Aus dem Chemischen Institut der Universität Breslau.]

(Eingegangen am 12. August 1909.)

In vorliegender Arbeit sollte die in der vorangehenden Arbeit mit Erfolg durchgeführte Reaktion zur Bildung von Pyrrolidinderivaten auf das Dihydrometanicotin angewendet werden, wobei man dann im Sinne folgender Gleichung Nicotin erwarten konnte:

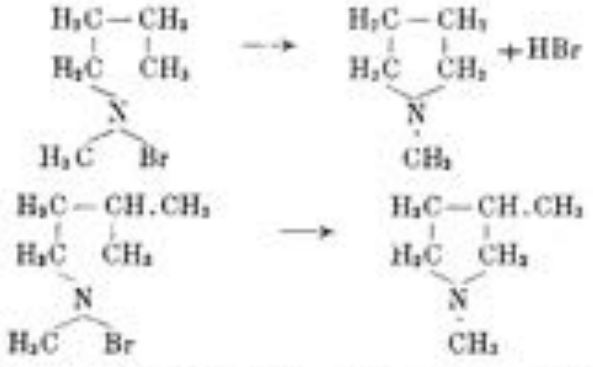


502. Karl Löffler und Curt Freytag:
Über eine neue Bildungsweise von *N*-alkylierten Pyrrolidinen.

[Aus dem Chemischen Institut der Universität Breslau.]

(Eingegangen am 12. August 1909.)

A. W. Hofmann[1]) erhielt durch Einwirkung von Brom in alkalischer Lösung auf Coniin ein Bromconiin, welches das Brom in der Imidgruppe substituiert enthält. Durch Einwirkung von konzentrierter Schwefelsäure bei 160° stellte er daraus unter Abspaltung von Bromwasserstoff ein Conicein dar, welches tertiär und gesättigt war. Er hielt die Base für α-Conicein. Lellmann stellte fest, daß diese Base nicht mit α-Conicein identisch ist, und nannte sie zur Unterscheidung von den übrigen Coniceinen δ-Conicein. Gleichzeitig sprach er die Vermutung aus, daß dem δ-Conicein folgende Formel zukommen dürfte:



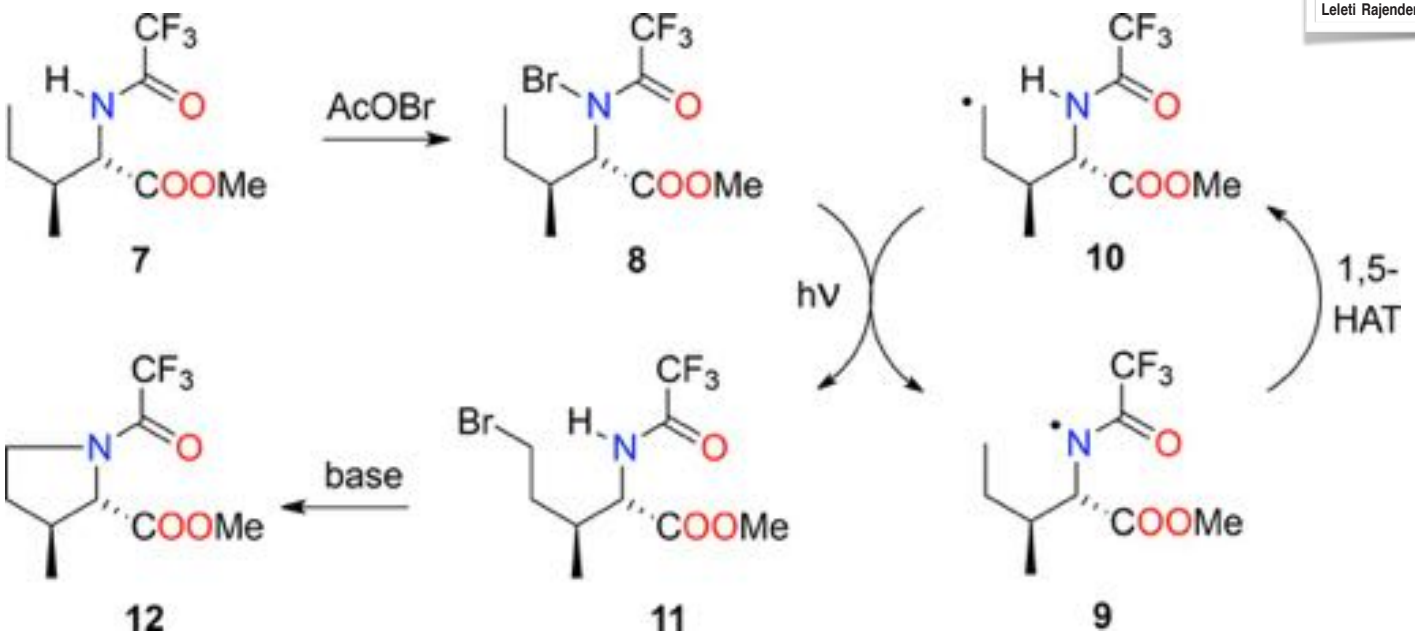
1909.

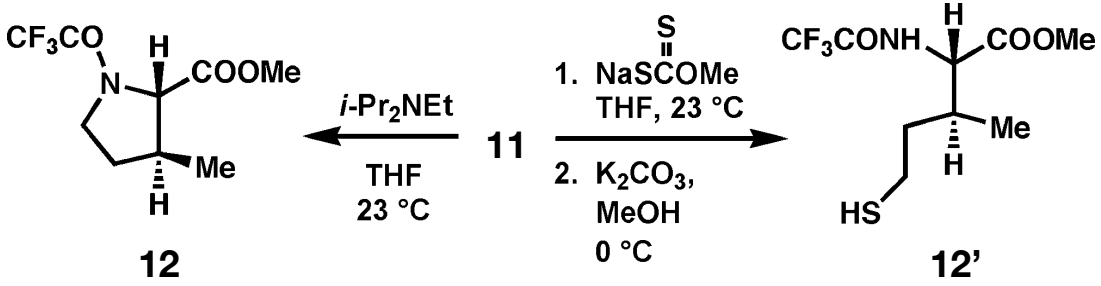
Corey

ORGANIC LETTERS
2006
Vol. 8, No. 13
2819–2821

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*



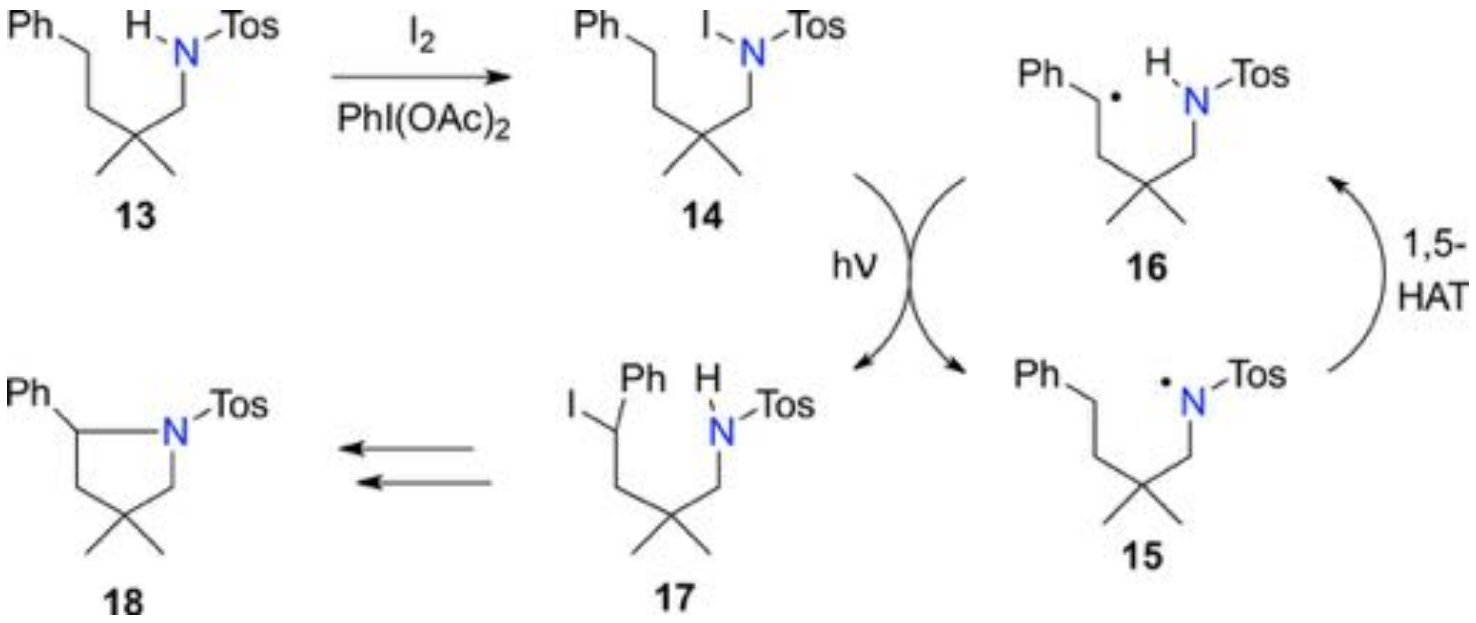


SYNTHESIS OF 1,4-EPIMINE COMPOUNDS. IODOSOBENZENE DIACETATE, AN EFFICIENT REAGENT FOR NEUTRAL NITROGEN RADICAL GENERATION

Tetrahedron Letters, Vol.26, No.20, pp 2493-2496, 1985

P. de Armas, R. Carrau, J.I. Concepción, C.G. Francisco, R. Hernández, and E. Suárez*

Suárez



Muñiz

Angewandte International Edition Chemie

Synthetic Methods

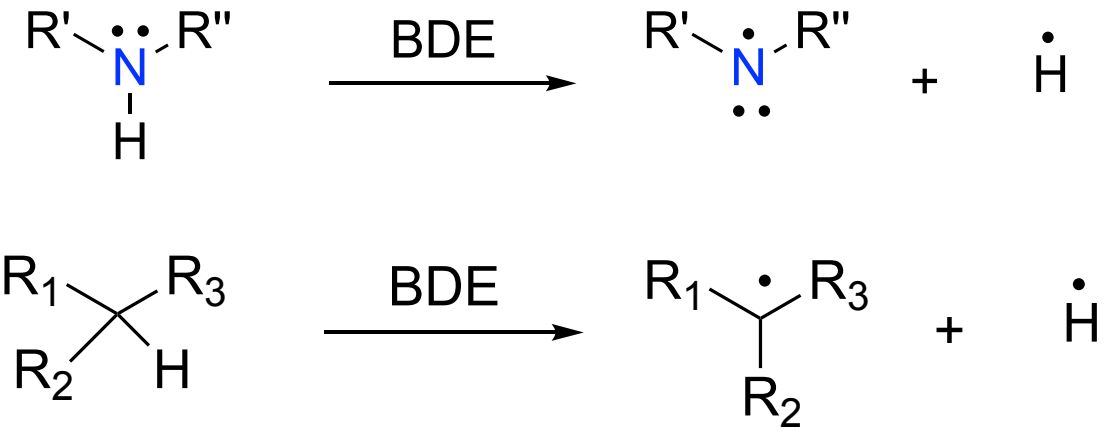
International Edition: DOI: 10.1002/anie.201501122
German Edition: DOI: 10.1002/ange.201501122

An Iodine-Catalyzed Hofmann–Löffler Reaction**

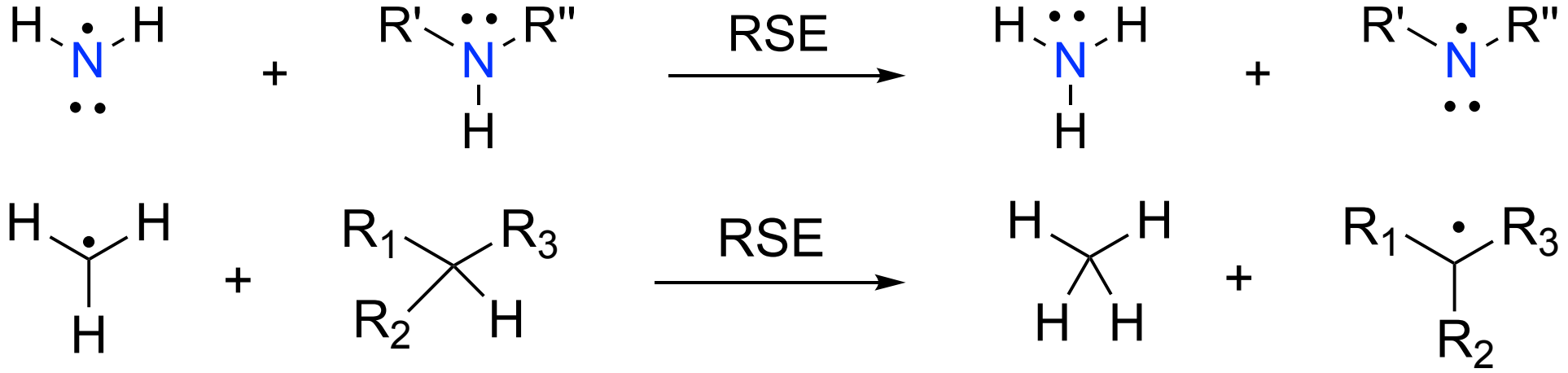
*Claudio Martínez and Kilian Muñiz**

Computational chemistry?

Thermodynamics



H_{298}@G3B3
H_{298}@G3(MP2)-RAD
H_{298}@RO-B2PLYP/G3MP2-Large



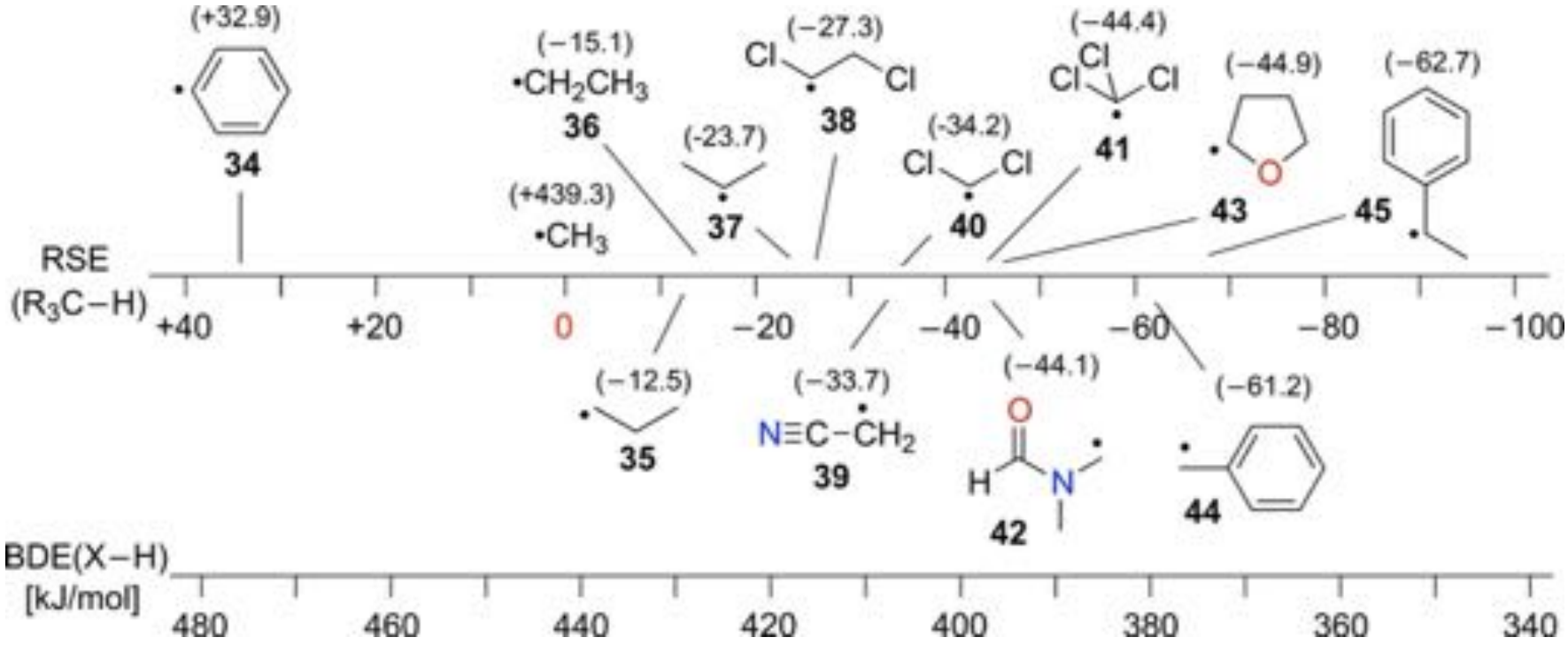
“Radical-ladders”

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

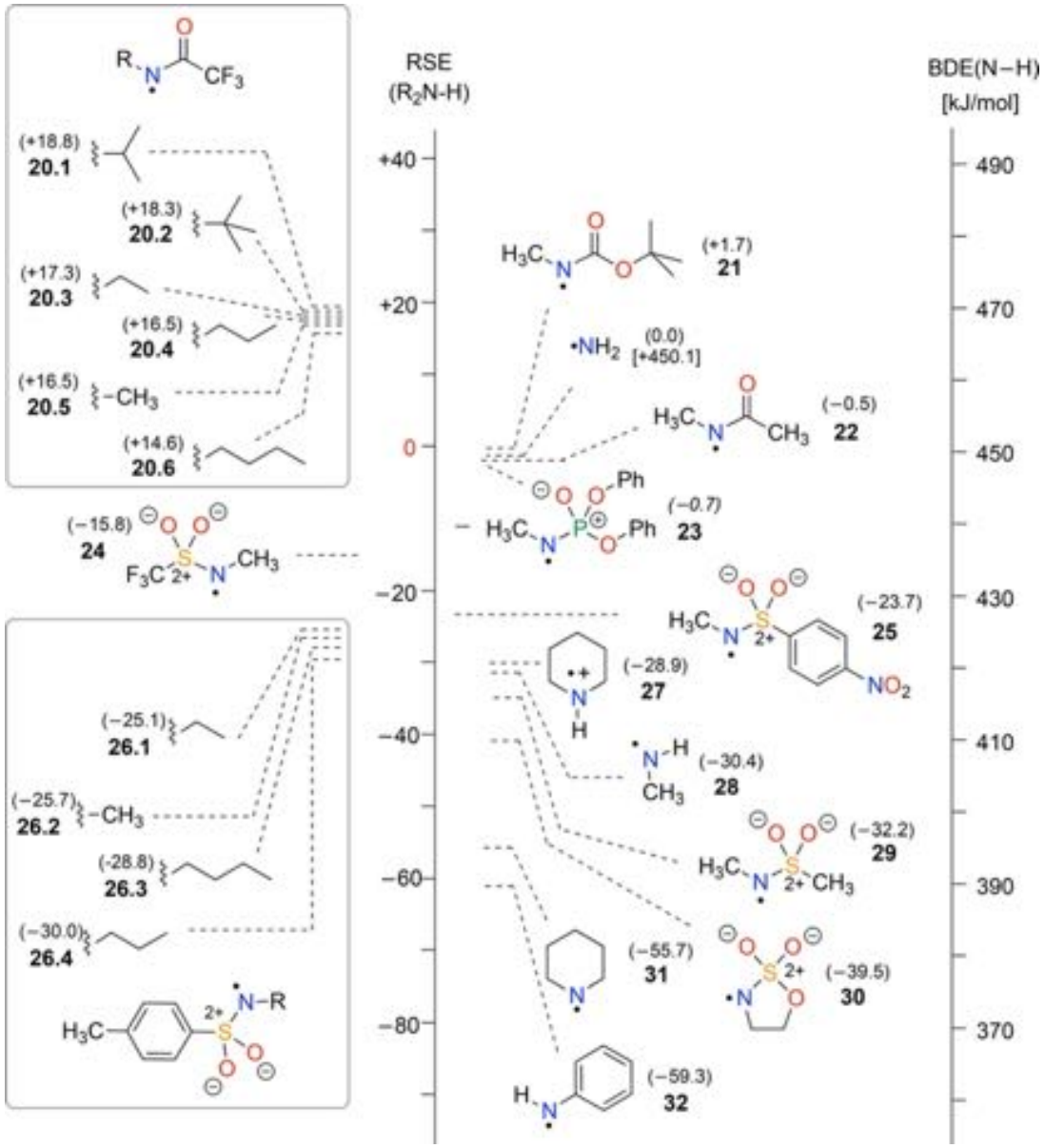
Very Important Publication

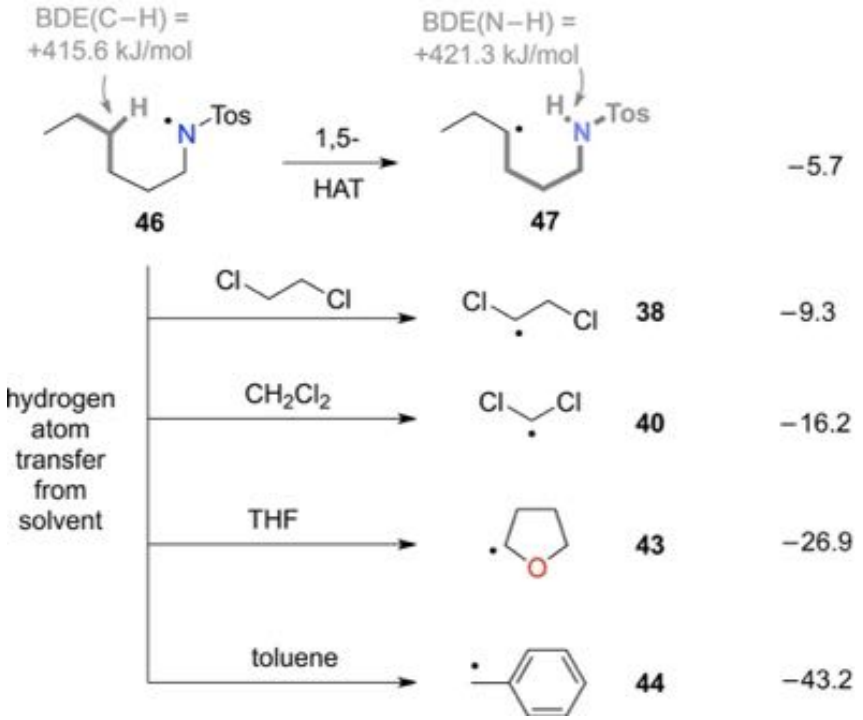
Radical Stability as a Guideline in C–H Amination Reactions

Davor Šakić[a] and Hendrik Zipse[b,*]



G16, H_{298}@G3B3//B3LYP/6-31G(d)





G16, H_{298}@G3B3//B3LYP/6-31G(d)

Back to basics
Nicotine re-synthesis

OL | Organic Letters

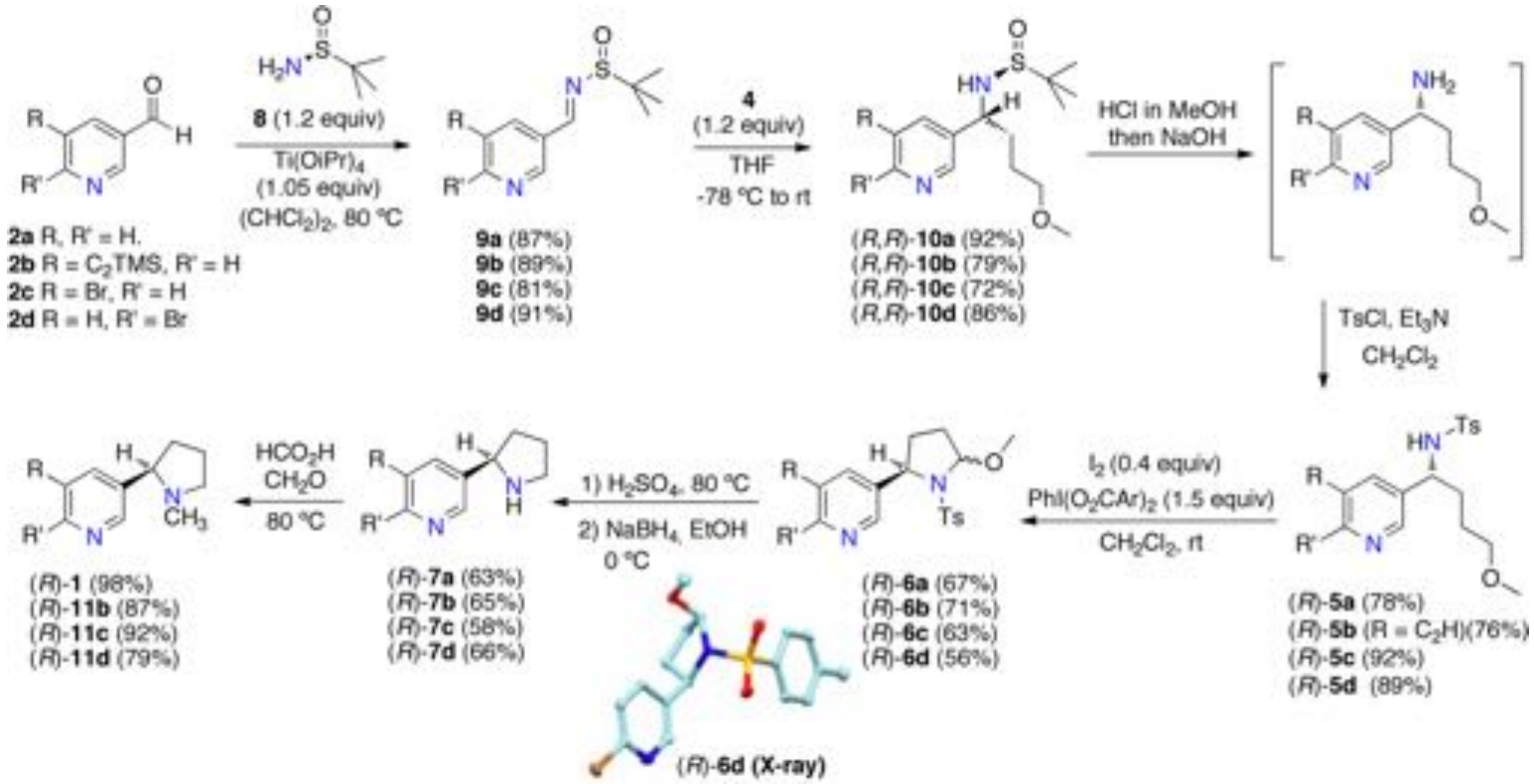
Letter

Cite This: *Org. Lett.* 2019, 21, 705−708

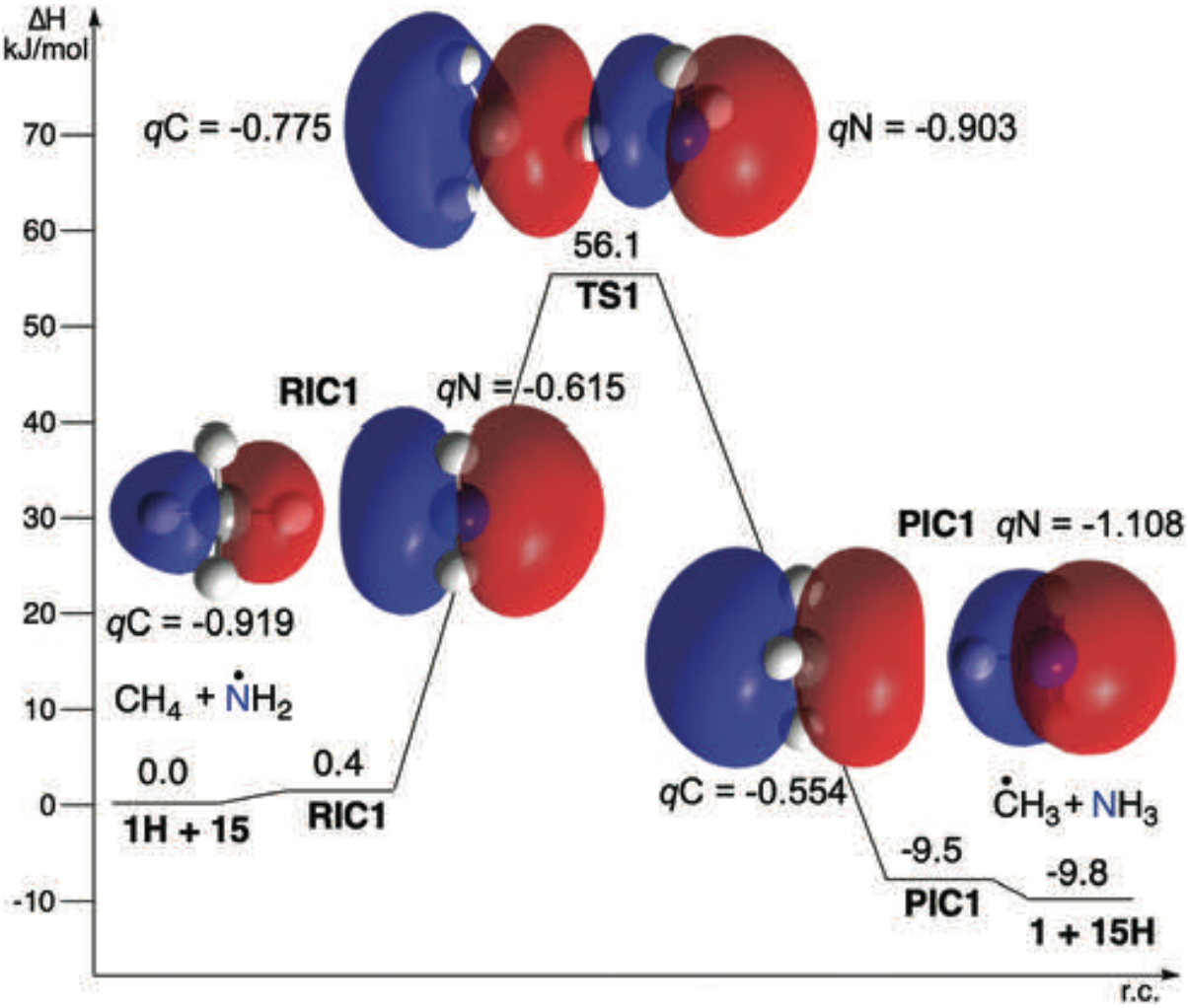
pubs.acs.org/OrgLett

Enantioselective Synthesis of Nicotine via an Iodine-Mediated Hofmann−Löffler Reaction

Estefanía Del Castillo[†] and Kilian Muñiz*[,†,‡]



Kinetics



Organic & Biomolecular Chemistry

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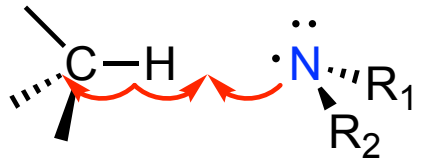
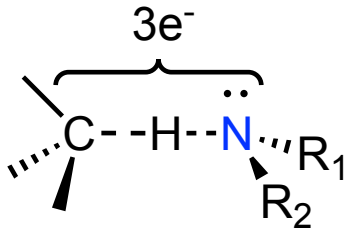
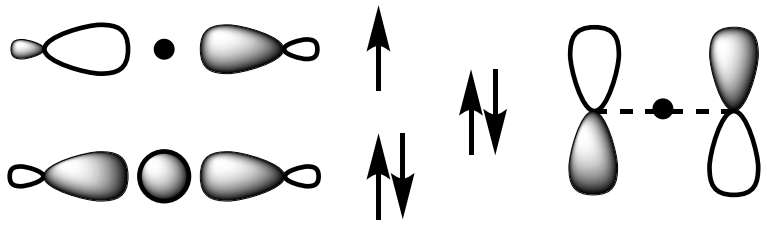
Cite this: DOI: 10.1039/d0ob02187c

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

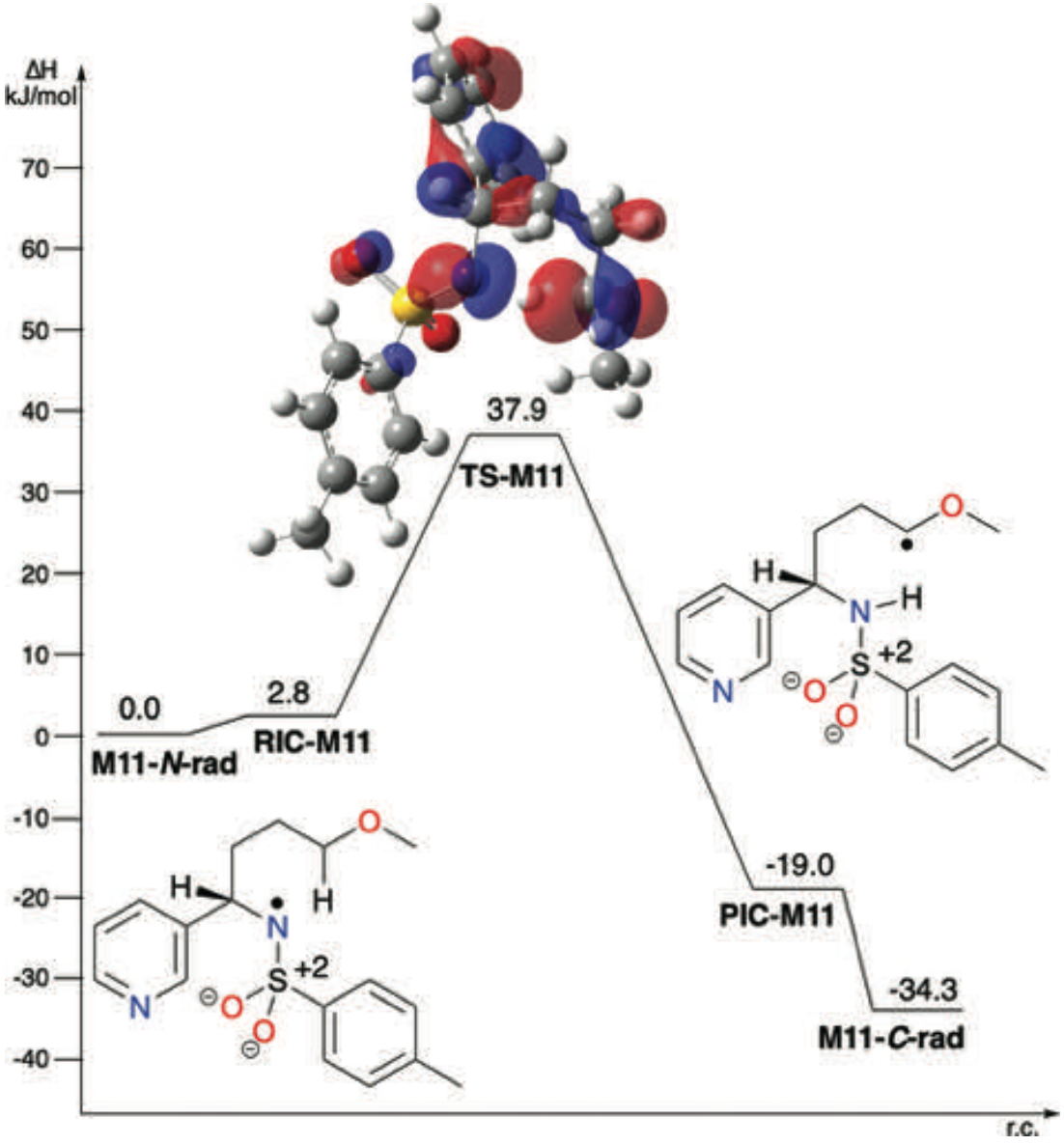
Sofia Shkunnikova,[a] Hendrik Zipse [b] and Davor Šakić *[a]







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



It works!

OL Organic Letters

Letter

Cite This: *Org. Lett.* 2019, 21, 705−708

pubs.acs.org/OrgLett

Enantioselective Synthesis of Nicotine via an Iodine-Mediated Hofmann−Löffler Reaction

Estefanía Del Castillo[†] and Kilian Muñiz*[,†,‡]

Organic & Biomolecular Chemistry

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Cite this: DOI: 10.1039/d0ob02187c

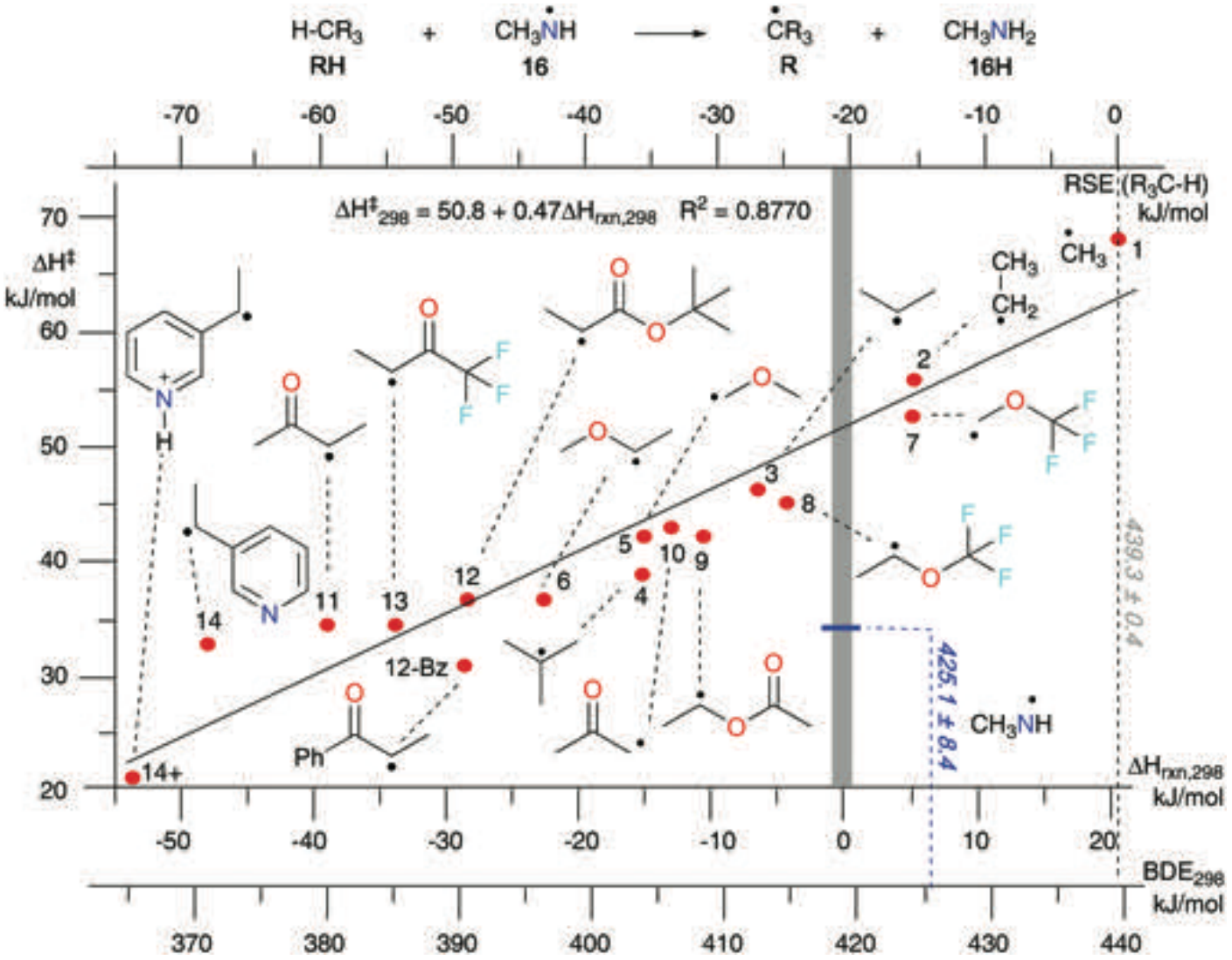
Role of substituents in the Hofmann−Löffler−Freytag reaction. A quantum-chemical case study on nicotine synthesis†‡

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

Can we improve?

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

Kinetics



Bell–Evans–Polanyi (BEP) principle

Organic & Biomolecular Chemistry

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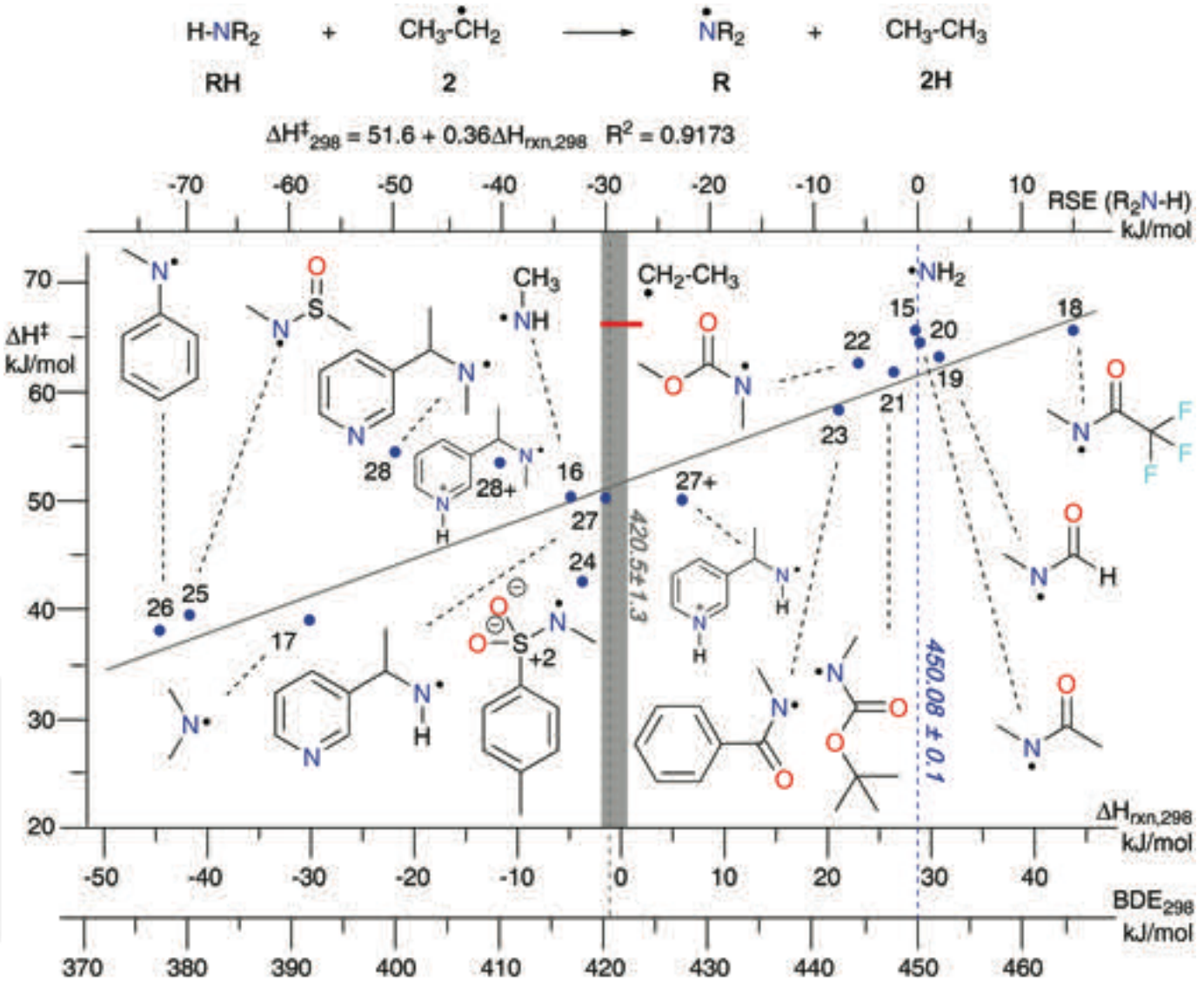
Sofia Shkunnikova,[a] Hendrik Zipse [b] and Davor Šakić *[a]

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

Kinetics

A bit contraintuitive



Organic & Biomolecular Chemistry
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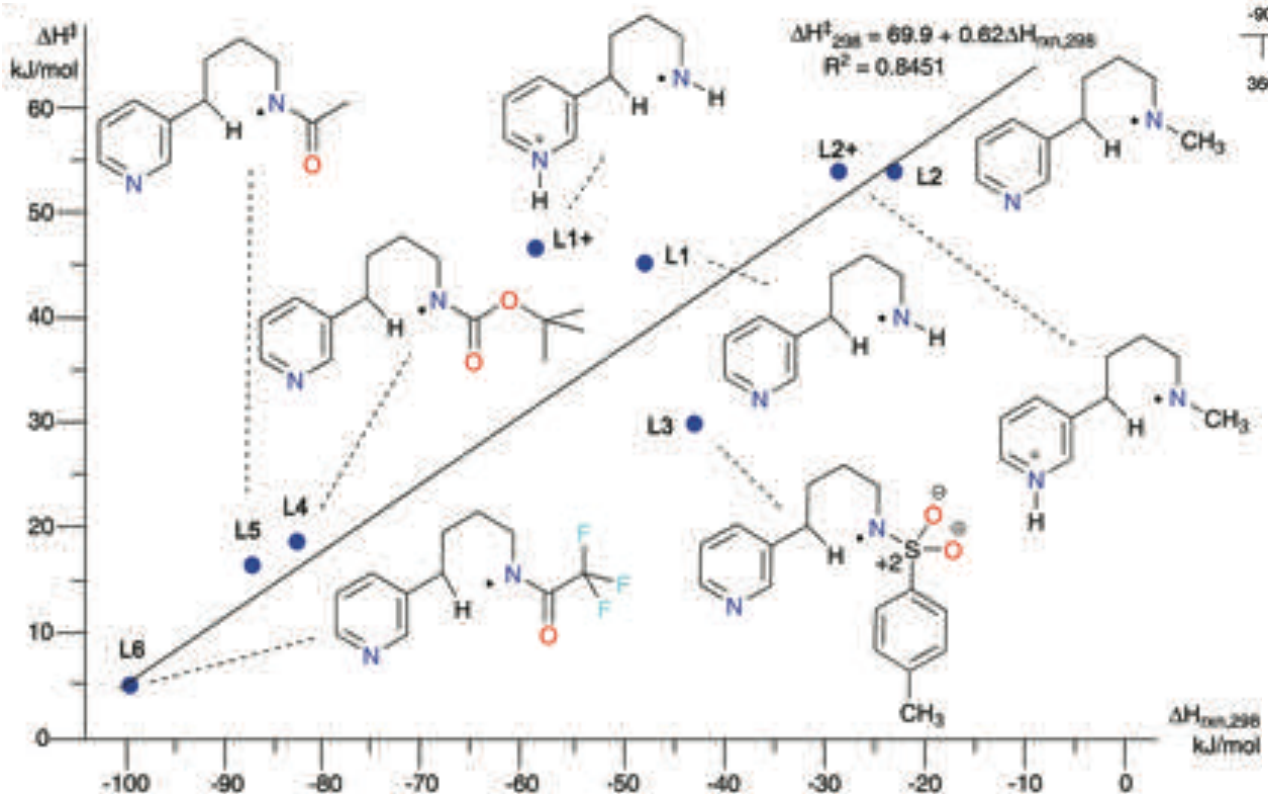
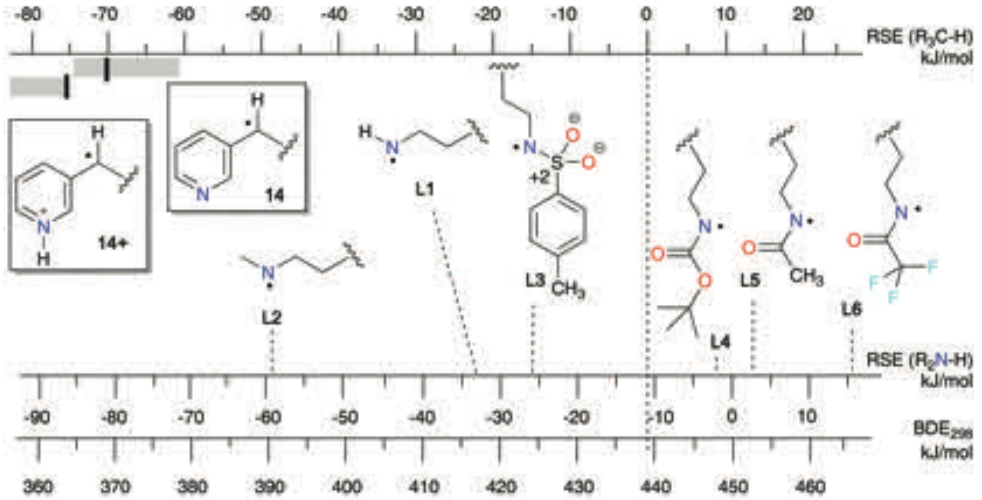
Sofia Shkunnikova,[a] Hendrik Zipse [b] and Davor Šakić *[a]

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

Thermodynamics & Kinetics

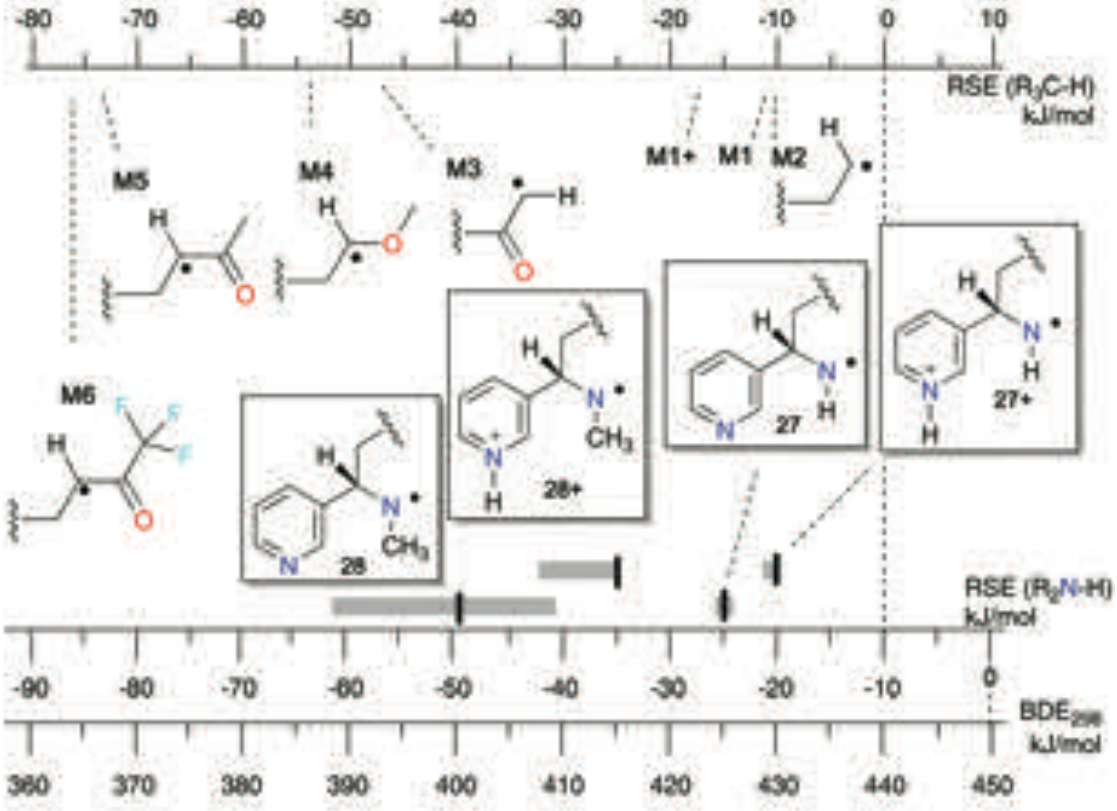


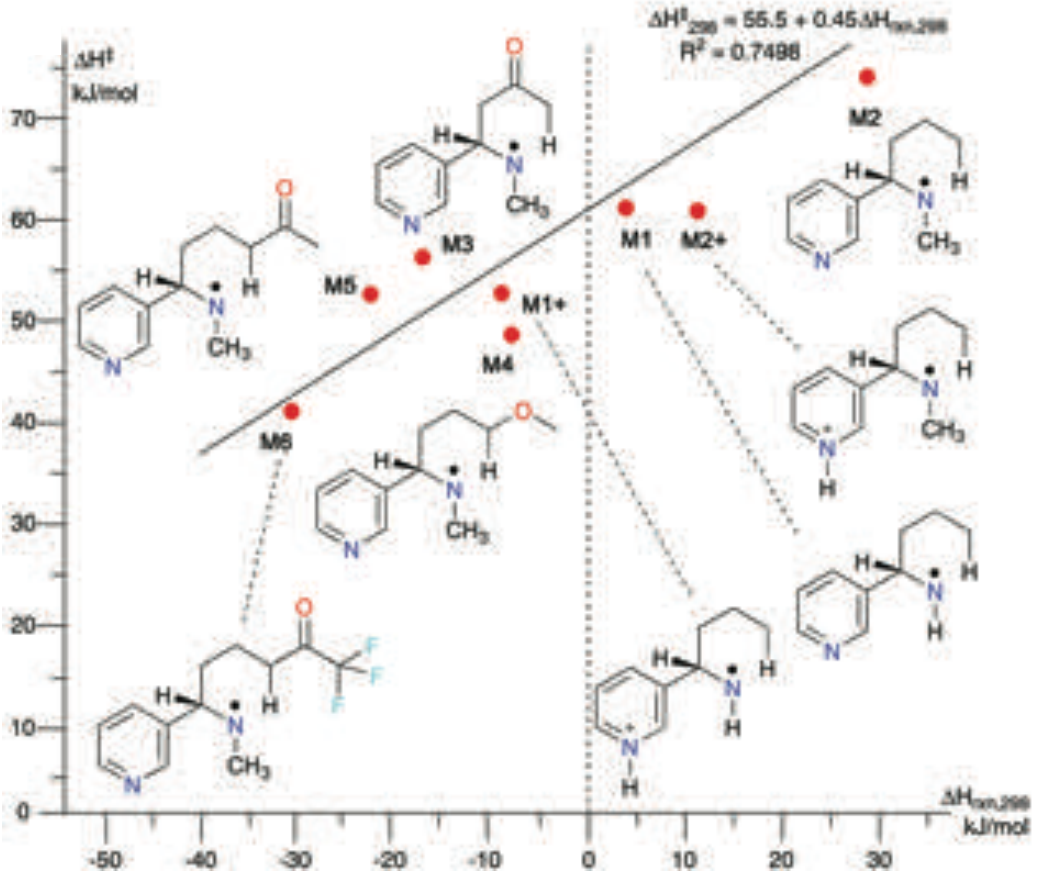


Corey again…

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

Thermodynamics & Kinetics





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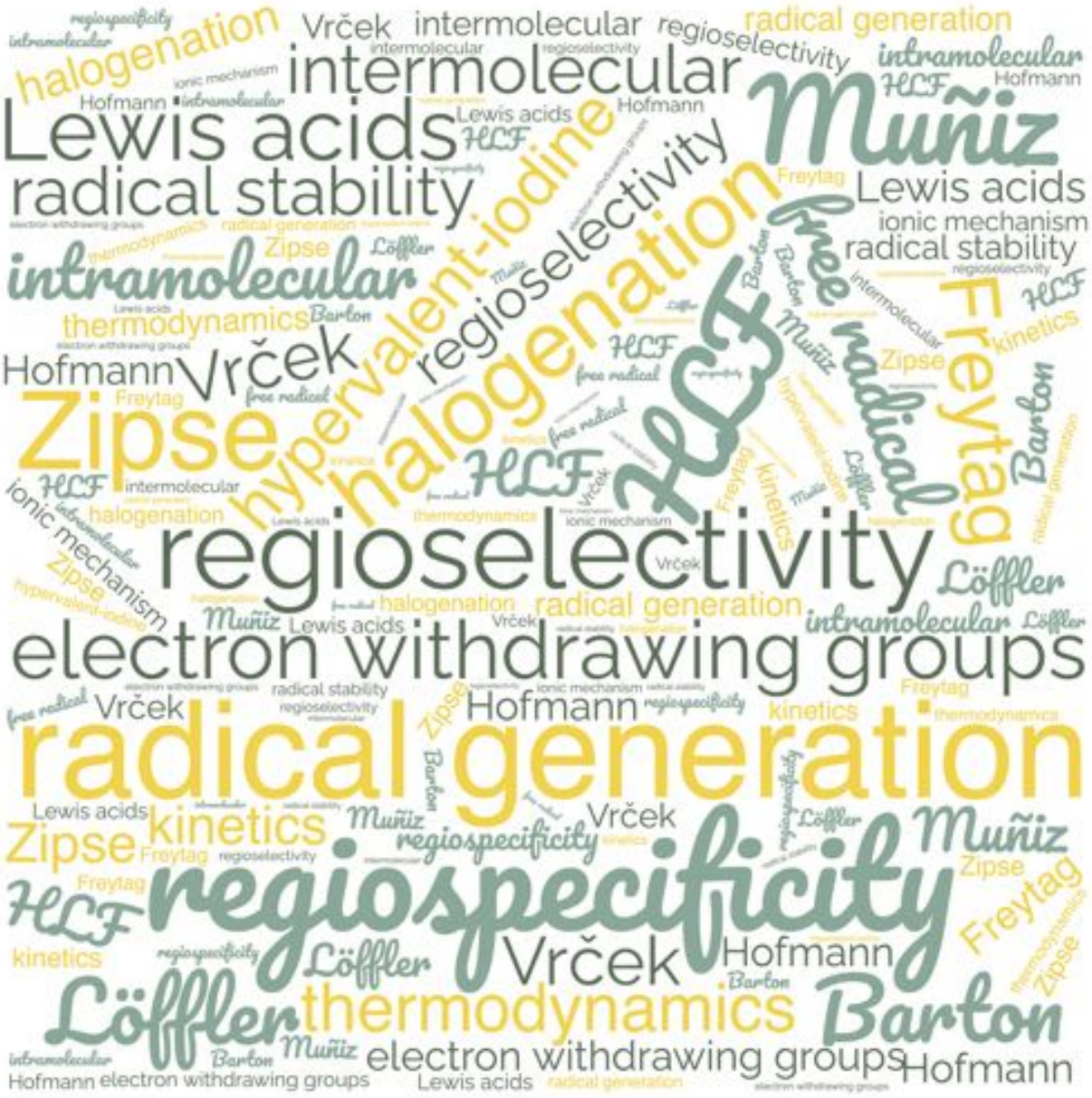
regiospecificity
halogenation
Vrček
intermolecular
regioselectivity
radical generation
intramolecular
HCF
Hofmann
Lewis acids
Muñiz
radical stability
Freytag
ionic mechanism
Zipse
Löffler
thermodynamics
Barton
free radical
kinetics
electron withdrawing groups

LIGHT RING

Regioselectivity PYRROLIDINE

Organic LETTERS
Letter
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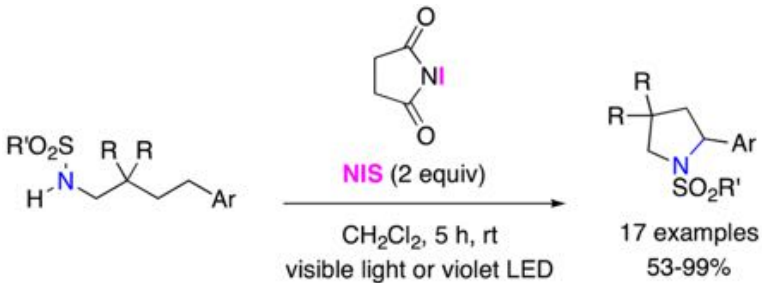
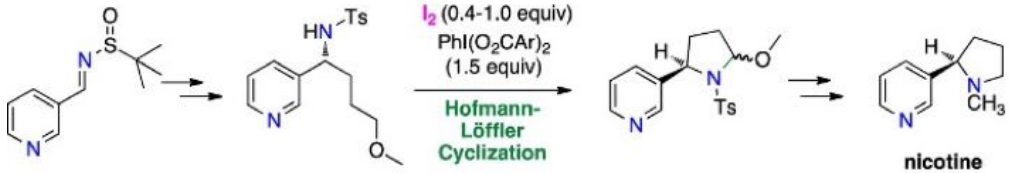
N-Iodosuccinimide-Promoted Hofmann–Löffler Reactions of Sulfonimides under Visible Light

Calvin Q. O'Broin,[†] Patricia Fernández,[†] Claudio Martínez,[†] and Kilian Muñiz*[,†,‡]





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Letter
OL Organic Letters
Cite This: Org. Lett. 2019, 21, 705–708
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Enantioselective Synthesis of Nicotine via an Iodine-Mediated Hofmann–Löffler Reaction

Estefanía Del Castillo[†] and Kilian Muñiz*[,†,‡]

Angewandte International Edition Chemie

Synthetic Methods

International Edition: DOI: 10.1002/anie.201501122
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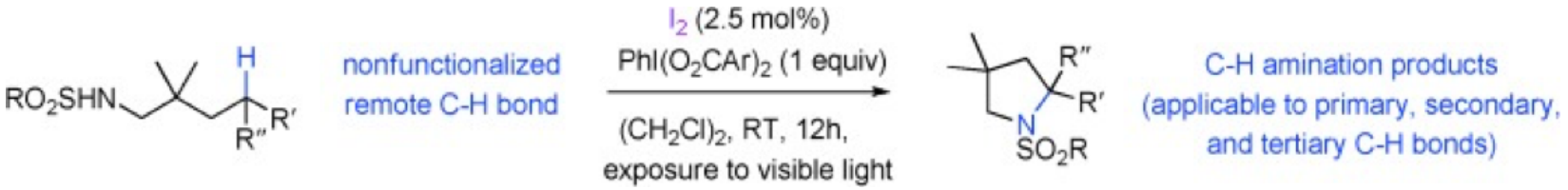
An Iodine-Catalyzed Hofmann–Löffler Reaction**

*Claudio Martínez and Kilian Muñiz**



Regioselectivity

PIPERIDINE

ACS Catalysis
Letter
Cite This: ACS Catal. 2019, 9, 7741−7745
pubs.acs.org/acscatalysis

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*[,†,§]

Chemical Science
ROYAL SOCIETY OF CHEMISTRY
EDGE ARTICLE
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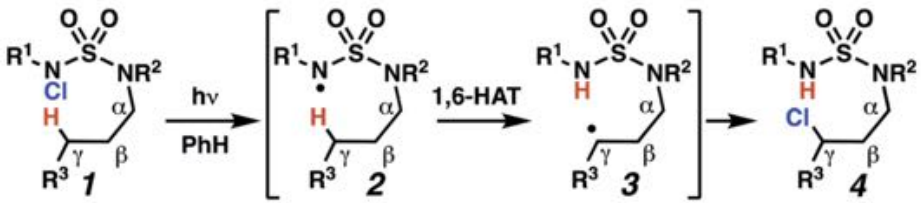
Cite this: Chem. Sci., 2020, 11, 217
All publication charges for this article have been paid for by the Royal Society of Chemistry

Sulfamides direct radical-mediated chlorination of aliphatic C–H bonds†

Melanie A. Short, Mina F. Shehata, Matthew A. Sanders and Jennifer L. Roizen*



ACS Catalysis
Letter
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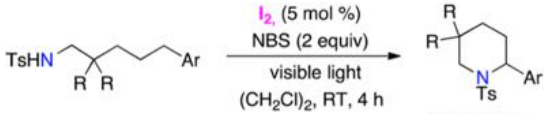
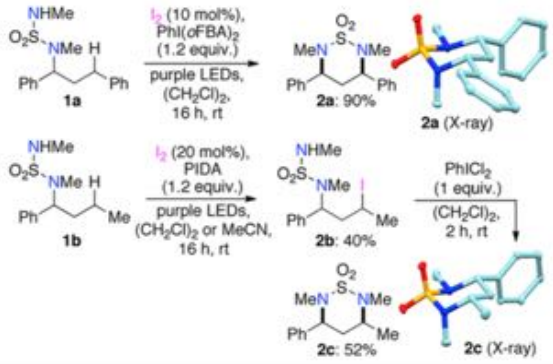
Selective Piperidine Synthesis Exploiting Iodine-Catalyzed $C_{sp}{}^3$–H Amination under Visible Light

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



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

Scheme 1. 1,3-Diamine Formation through Hofmann–Löffler Reaction: Initial Substrate Exploration

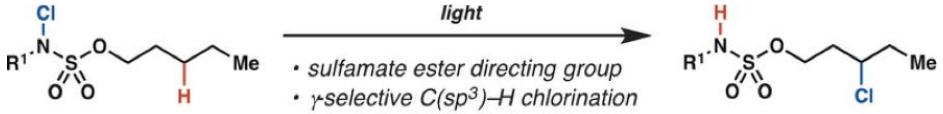


Angewandte International Edition Chemie
GDCh
A Journal of the German Chemical Society
Communication

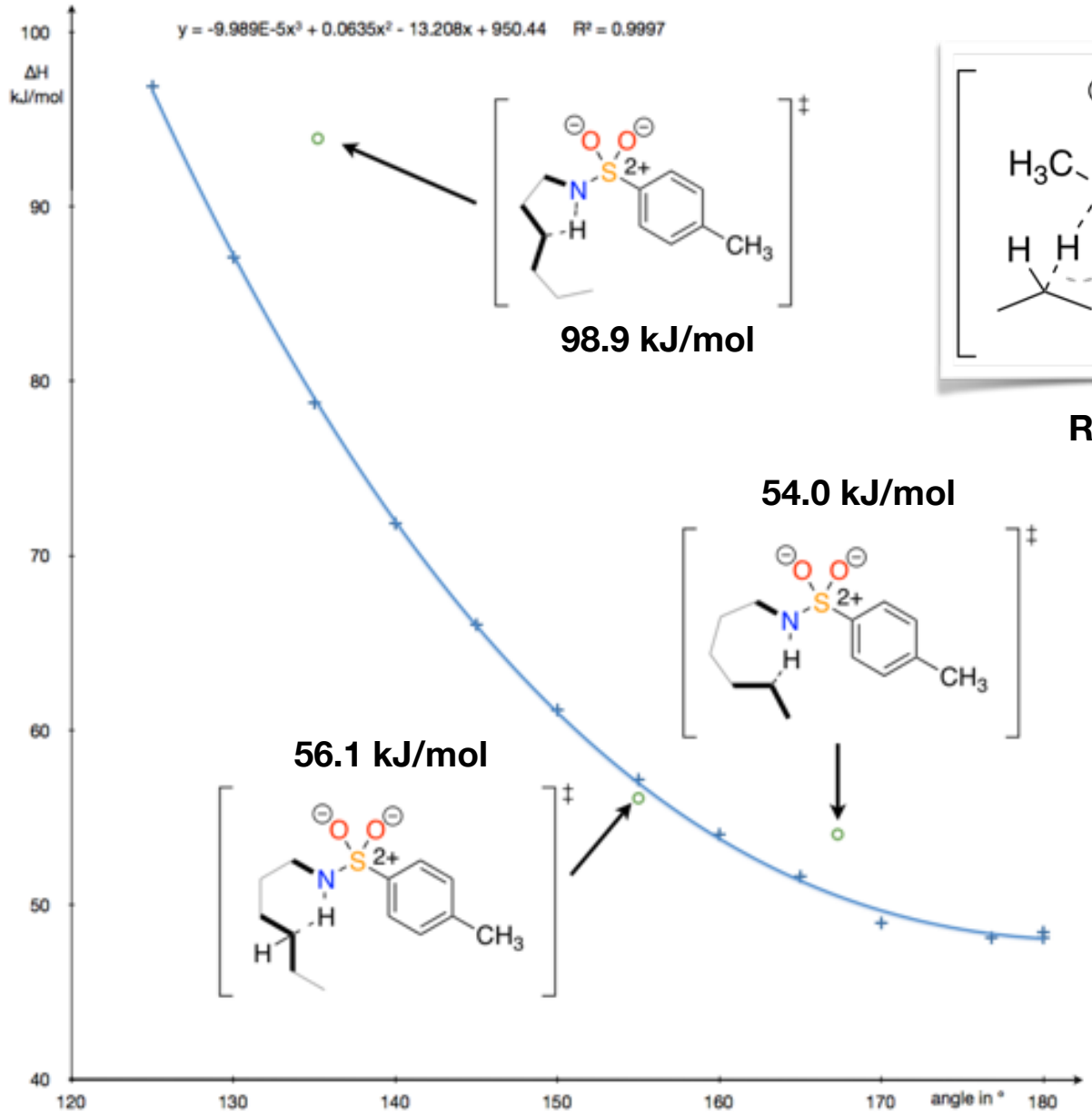
Sulfamate Esters Guide Selective Radical-Mediated Chlorination of Aliphatic C–H Bonds

Melanie A. Short, J. Miles Blackburn, Prof. Dr. Jennifer L. Roizen

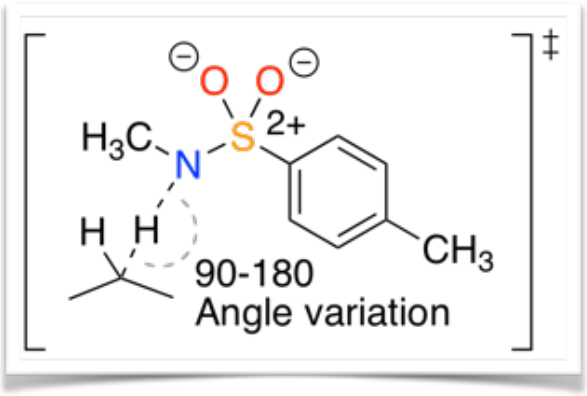
First published: 02 November 2017 | https://doi.org/10.1002/anie.201710322 | Citations: 86



- *sulfamate ester directing group*
- *γ-selective C(sp³)–H chlorination*
- *1°, 2°, and 3° C–H bonds*



98.9 kJ/mol



Regioselective?

54.0 kJ/mol

56.1 kJ/mol

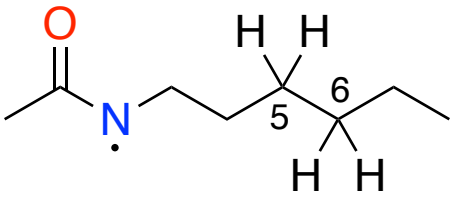
Thorpe-Ingold effect

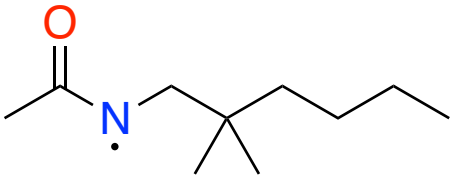
Compression of angle hypothesis

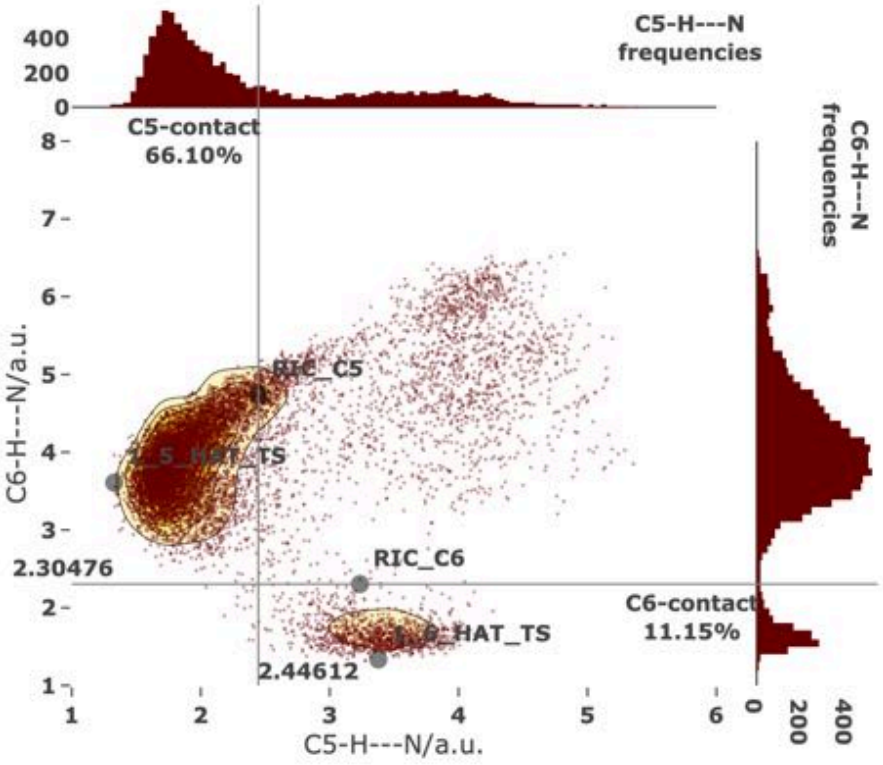
Reactive rotamer hypothesis

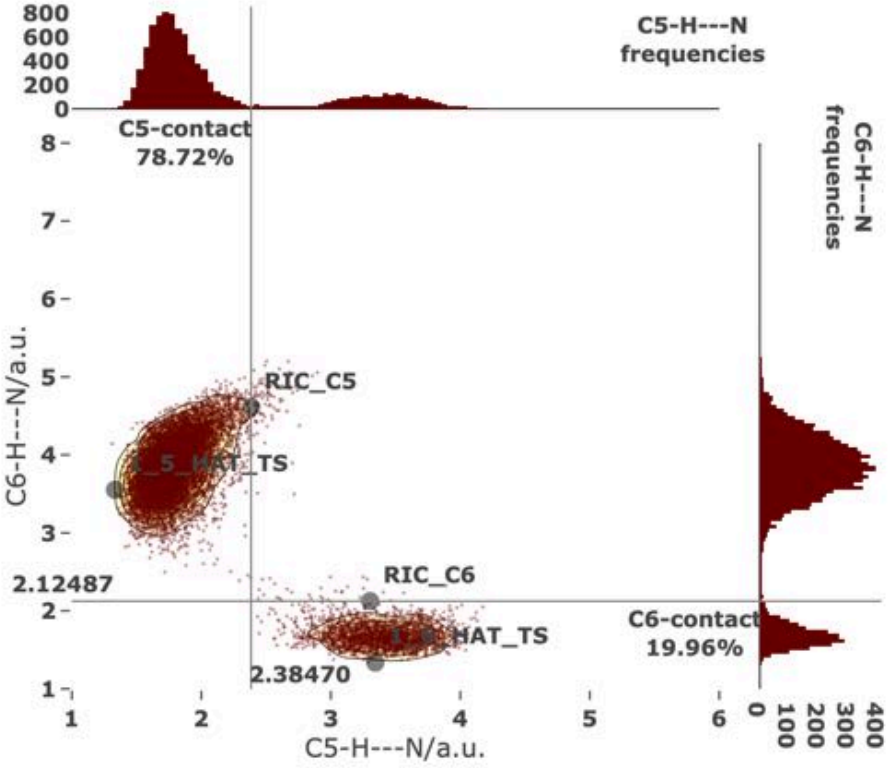
Reactive rotamer

Counting contacts



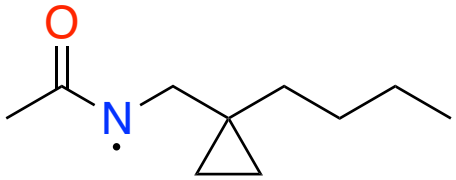


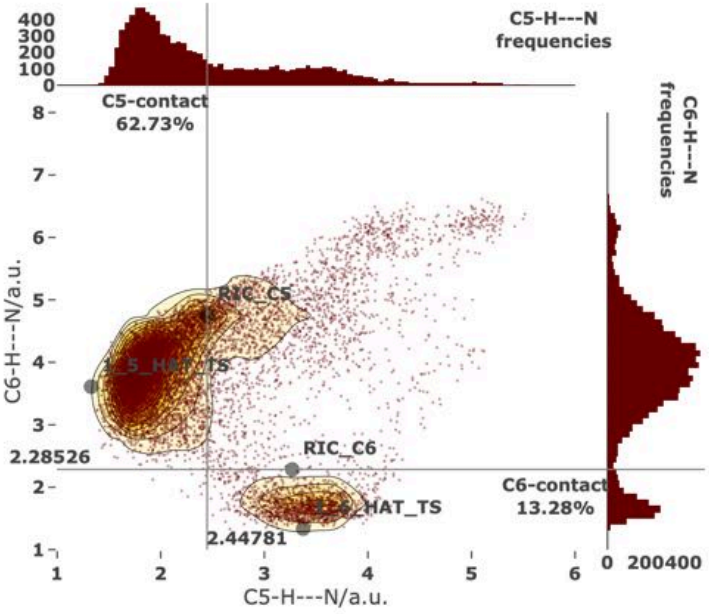


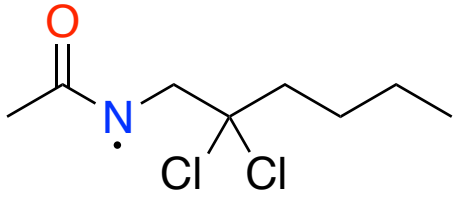


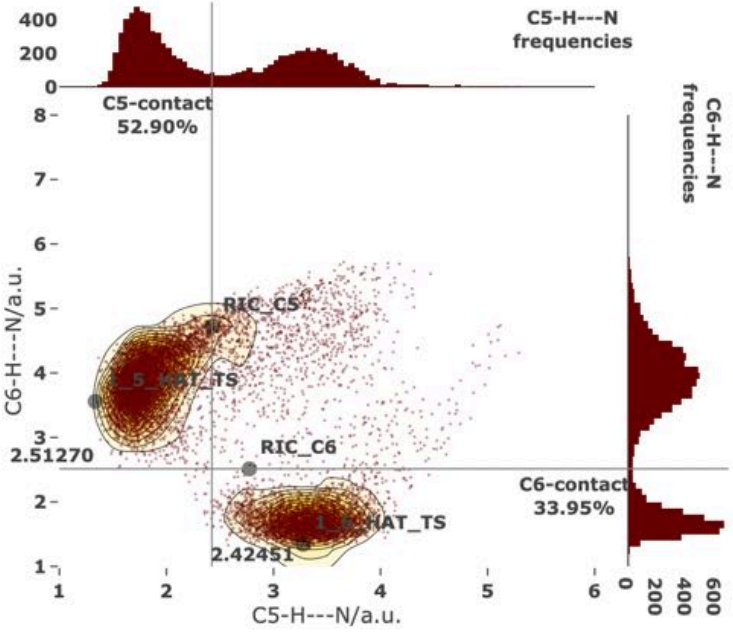
XTB @GFN2, SHAKE=ON, HMASS=4

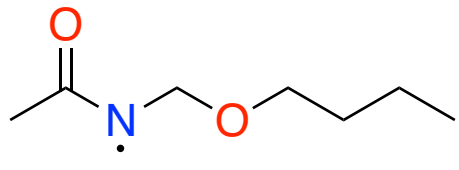
Counting contacts

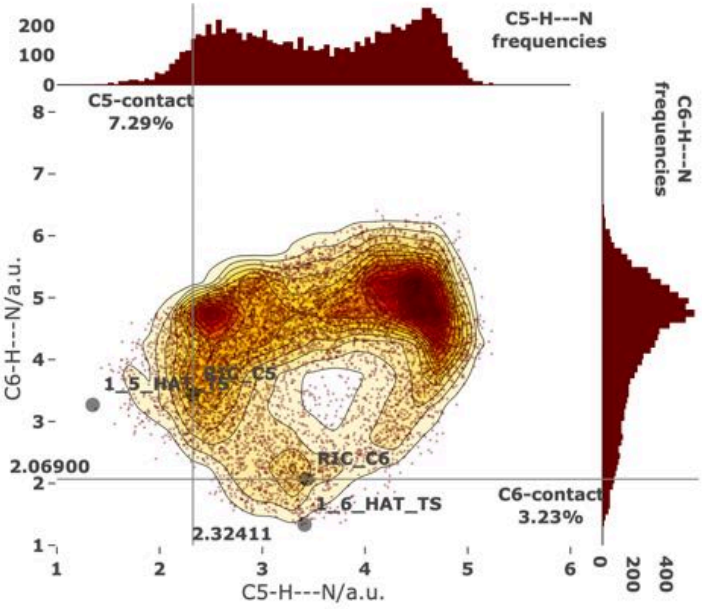






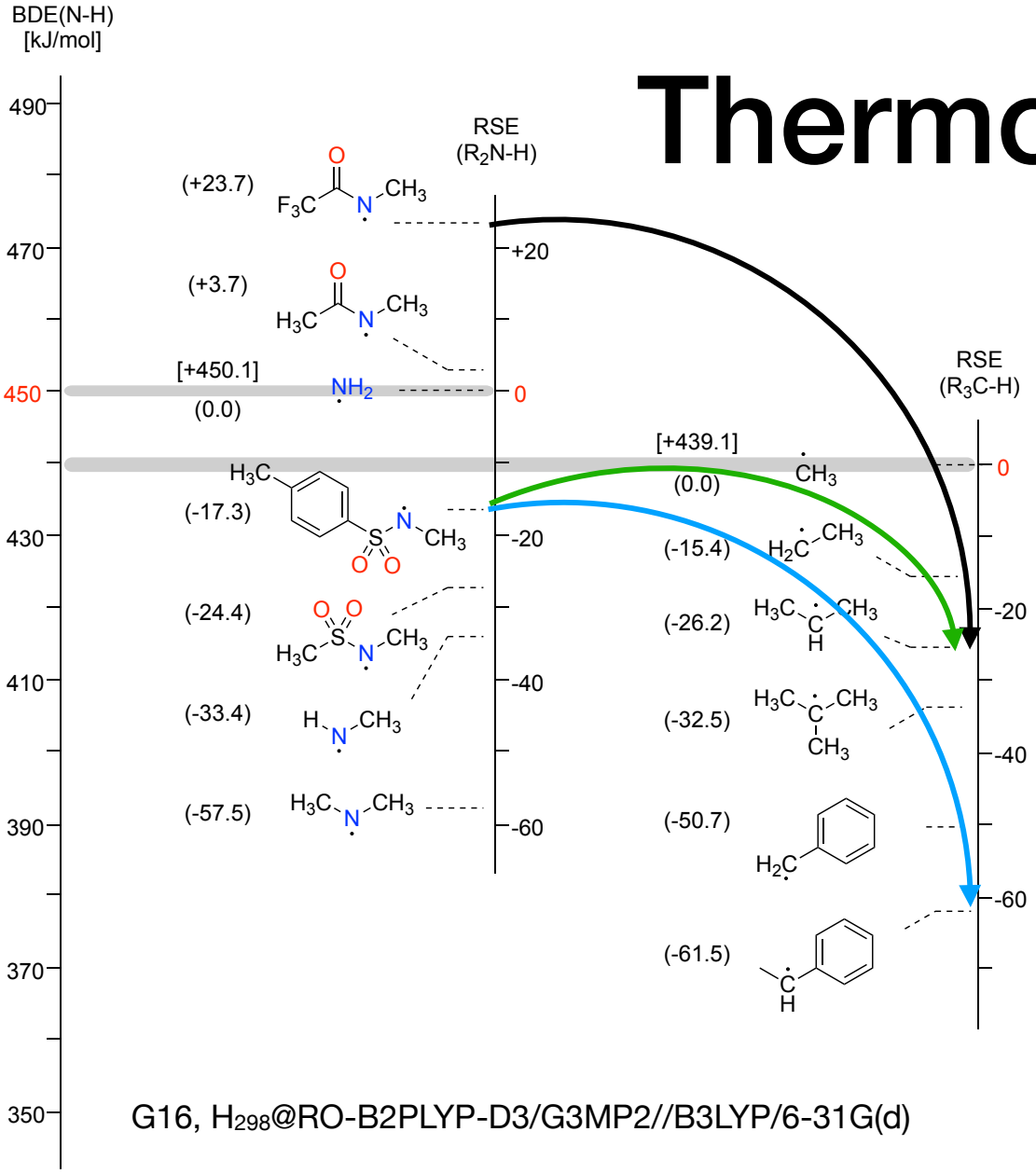






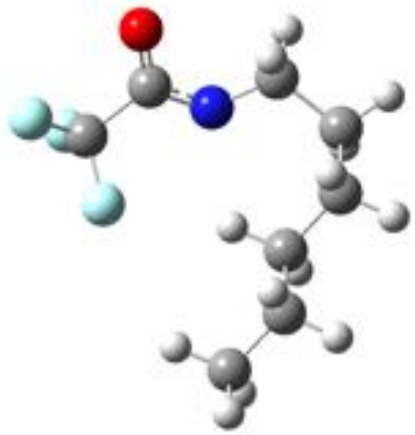
XTB @GFN2, SHAKE=ON, HMASS=4

Thermodynamics AGAIN!



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

_N_-triflouroacetyl-hexylamine

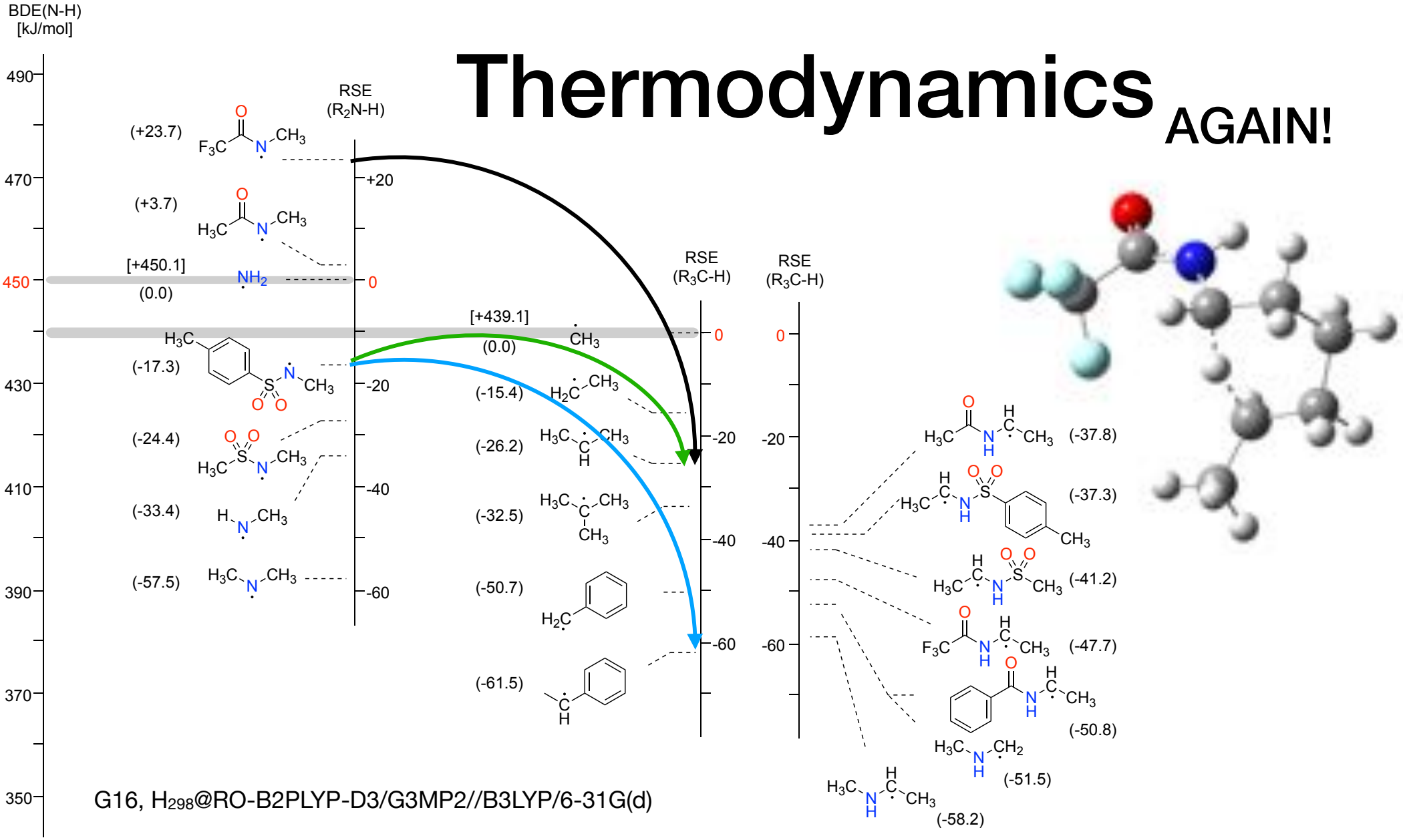


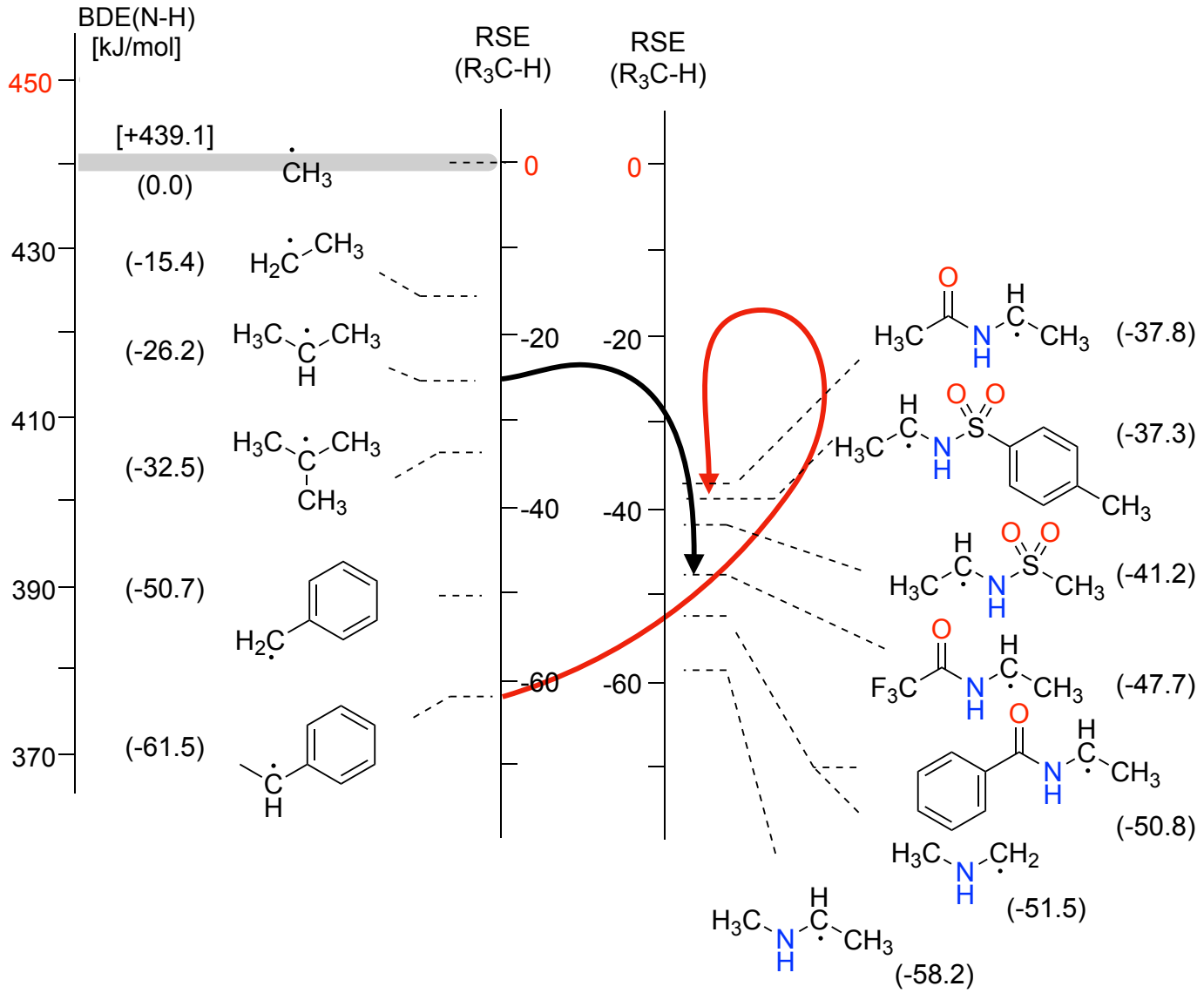
	$\Delta H^{\ddagger}_{298}$ kJ/mol	$\Delta H_{rx,298}$ kJ/mol
1,5-HAT	36.6	-37.9
1,6-HAT	38.0	-30.3

_N_-tosyl-(5-phenyl)hexylamine

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

Thermodynamics AGAIN!





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
REVERSE 1,5-HAT	57.6	-15.5

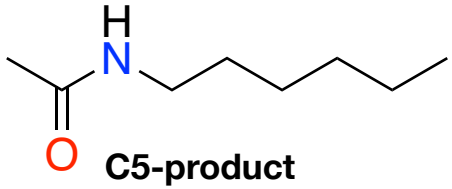
_N_-tosyl-(5-phenyl)hexylamine

	$\Delta H^{\ddagger}_{298}$ kJ/mol	$\Delta H_{rx,298}$ kJ/mol
REVERSE 1,5-HAT	88.1	25.0

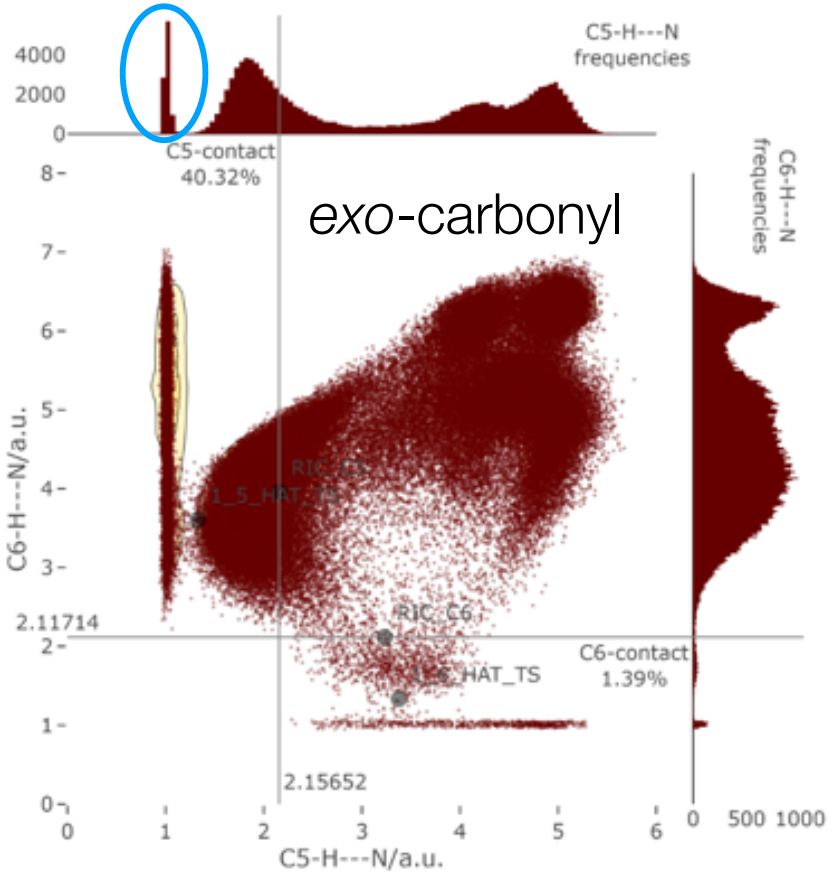
NEW STRATEGIES

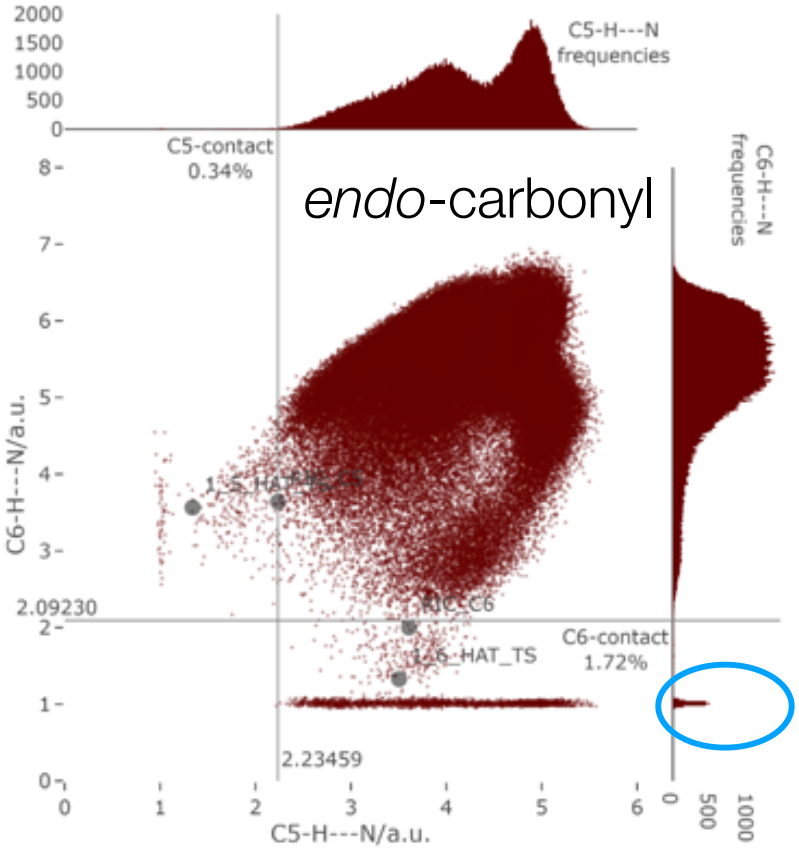
Positon of activating group

exo- vs. *endo-*

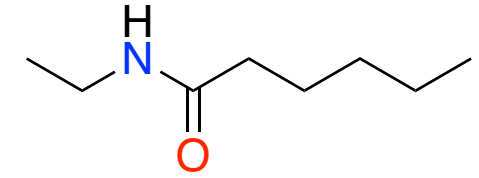


C5-product



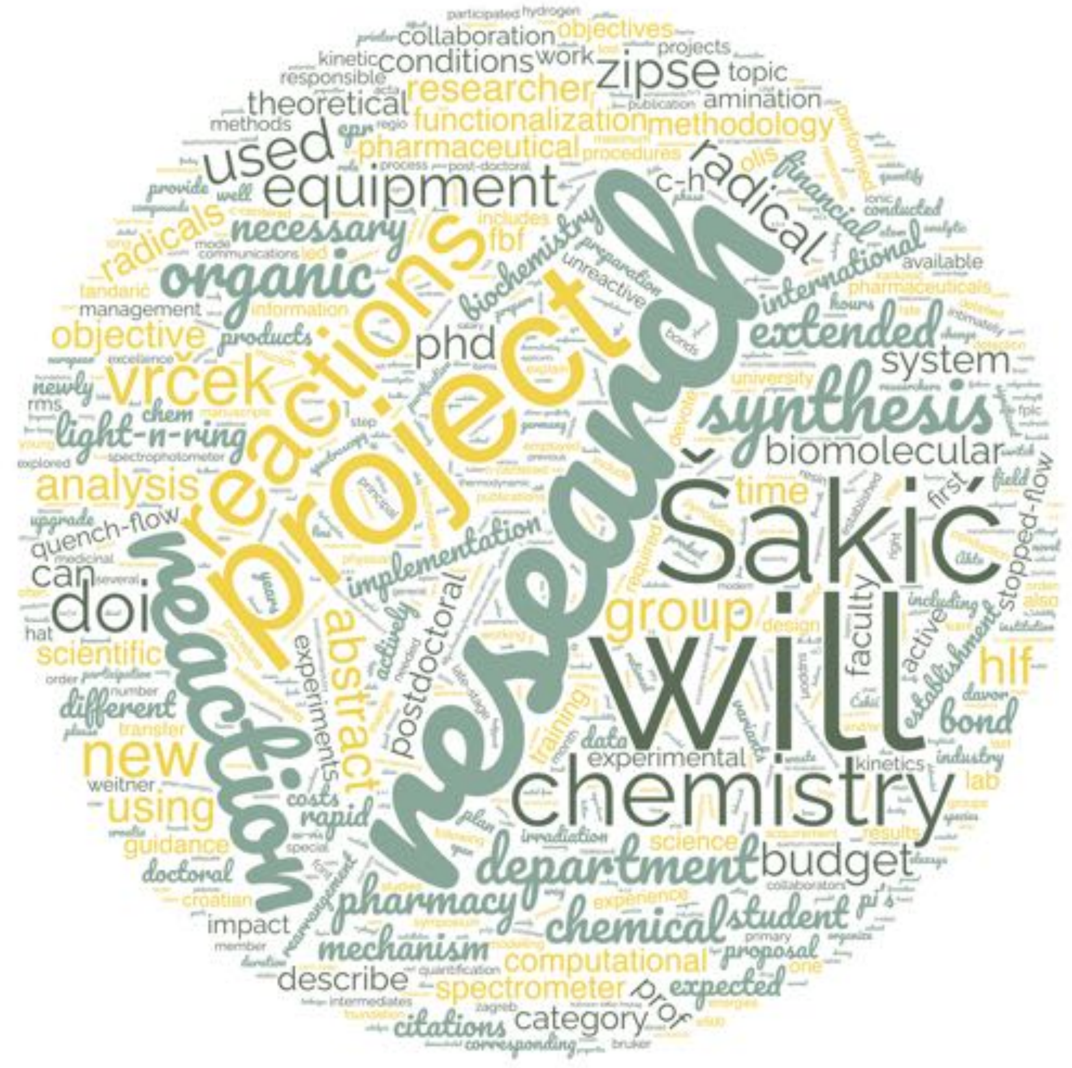


C6-product



Poster session @Zubčić

XTB @GFN2
SHAKE=OFF
HMASS=2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quench-flow
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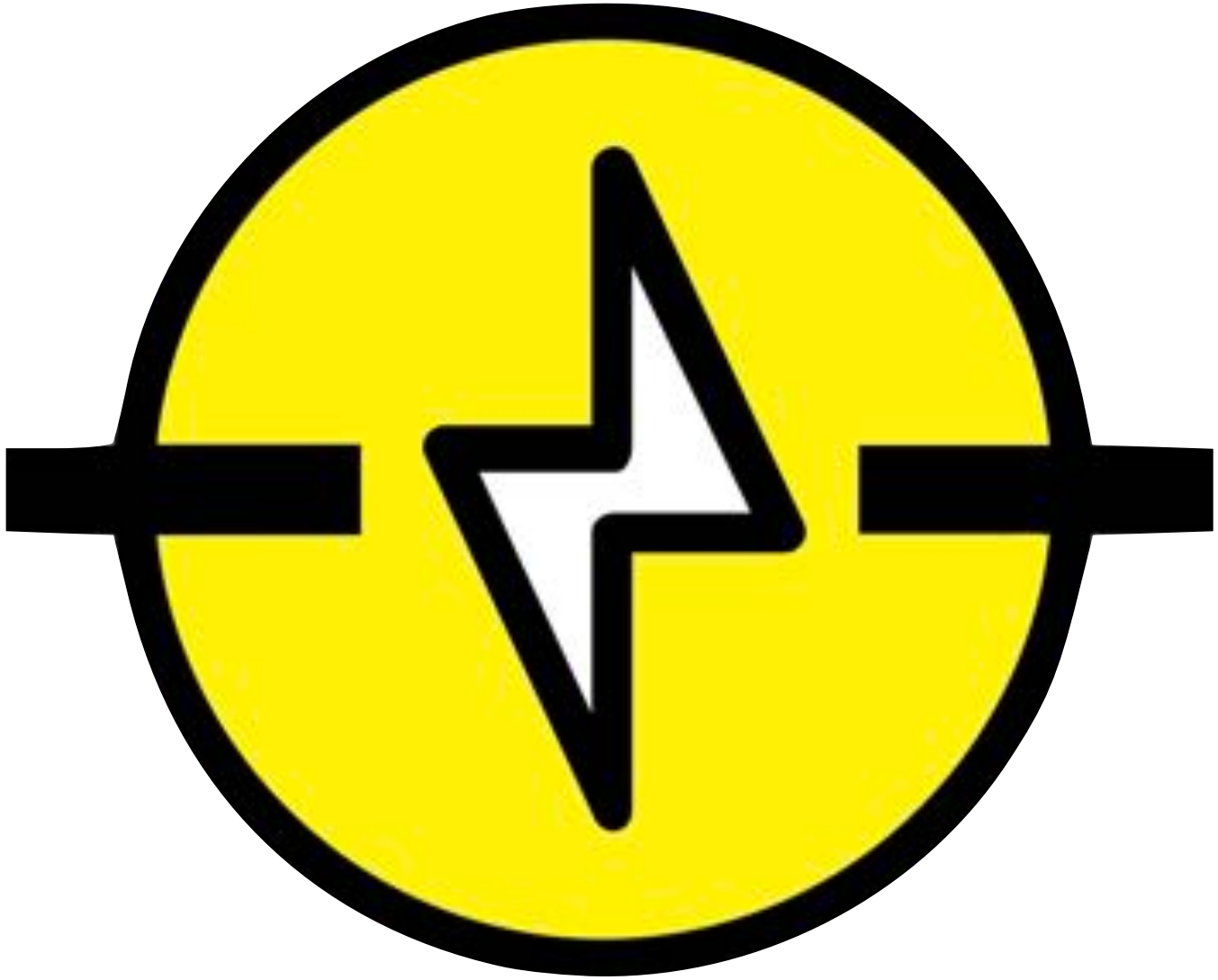
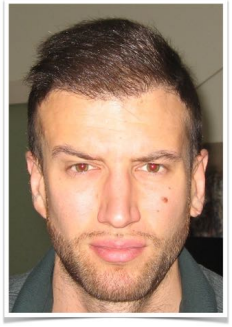


LIGHT RING

Thank you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