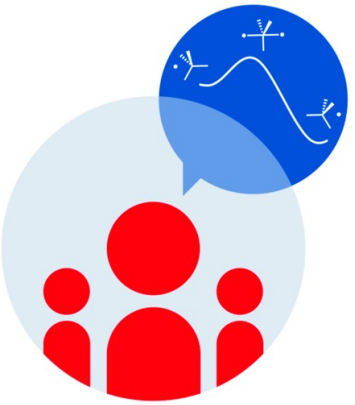
ESOR2023
Amsterdam



Regioselectivity in the Hofmann–Löffler–Freytag Reaction

A Computational Analysis of Rearrangement Reactions

Davor Šakić

LIGHT RING

HrZZ
Croatian Science Foundation

Hofmann Löffler–Freytag

537. A. W. Hofmann: Nachträgliches über die Einwirkung des Broms in alkalischer Lösung auf Amide.

[Aus dem Berliner Univ.-Laborat. I. No. DCXIV.]

[Sechste Mittheilung.] [1])

(Eingegangen am 20. August.)

Die Darstellung primärer aliphatischer Monamine nach dem von mir vor einigen Jahren angegebenen Verfahren — Behandlung der Säureamide mit Brom in alkalischer Lösung — ist in letzter Zeit im hiesigen Laboratorium mehrfach Gegenstand von Versuchen gewesen. Hr. Erich Lutz hat die gedachte Methode auf das Amid der Myristinsäure angewendet und zunächst das Amin der Tredecanreihe dargestellt, dieses aber durch alkalische Bromlösung nach einer noch jüngst erst beschriebenen Reaction [2]) in das zugehörige Nitril übergeführt, welches, in Amid verwandelt, Amin, Nitril, Amid und Säure der Dodecanreihe geliefert hat. Hr. Paul Ehestädt hat die Untersuchung an der Stelle aufgenommen, an welcher Hr. Lutz den Versuch abbrach; indem er, von dem Amid der Laurinsäure ausgehend, durch das Amin, Nitril und Amid der Undecanreihe hindurch zu dem Amin der Decanreihe gelangte, um dieses schliesslich bis zur Nonoxylsäure abzubauen. Die genannten Beobachter werden demnächst über ihre Versuche Mittheilung machen.

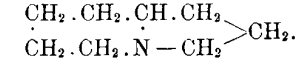
1883.

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:



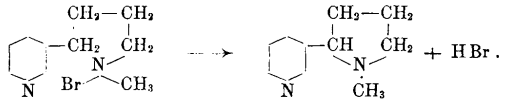
Die Richtigkeit dieser Anschauung wurde von Löffler und Kaim [2]) bewiesen. Beim Erwärmen von α-Piperidylpropionsäure auf 200° erhielten sie das Lactim dieser Säure, welches durch Reduktion mit Natrium und Alkohol in das »Piperolidin« überging, dem dieselbe Zusammensetzung und Konstitution zukommt, wie sie von Lellmann für das δ-Coniciin vermutet wurde und in obiger Formel zum Ausdruck gelangt. Die Eigenschaften dieser Base stimmten überein mit einem aus inaktivem Coniin nach der Hofmannschen Methode gewonnenem inaktiven δ-Conicein. Dadurch war bewiesen, daß das am Stickstoff bromierte Coniin beim Erhitzen mit konzentrierter Schwefelsäure Bromwasserstoff unter Schließung eines Pyrrolidinringes abspaltet.

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

[Aus dem Chemischen Institut der Universität Breslau.]

(Eingegangen am 12. August 1909.)

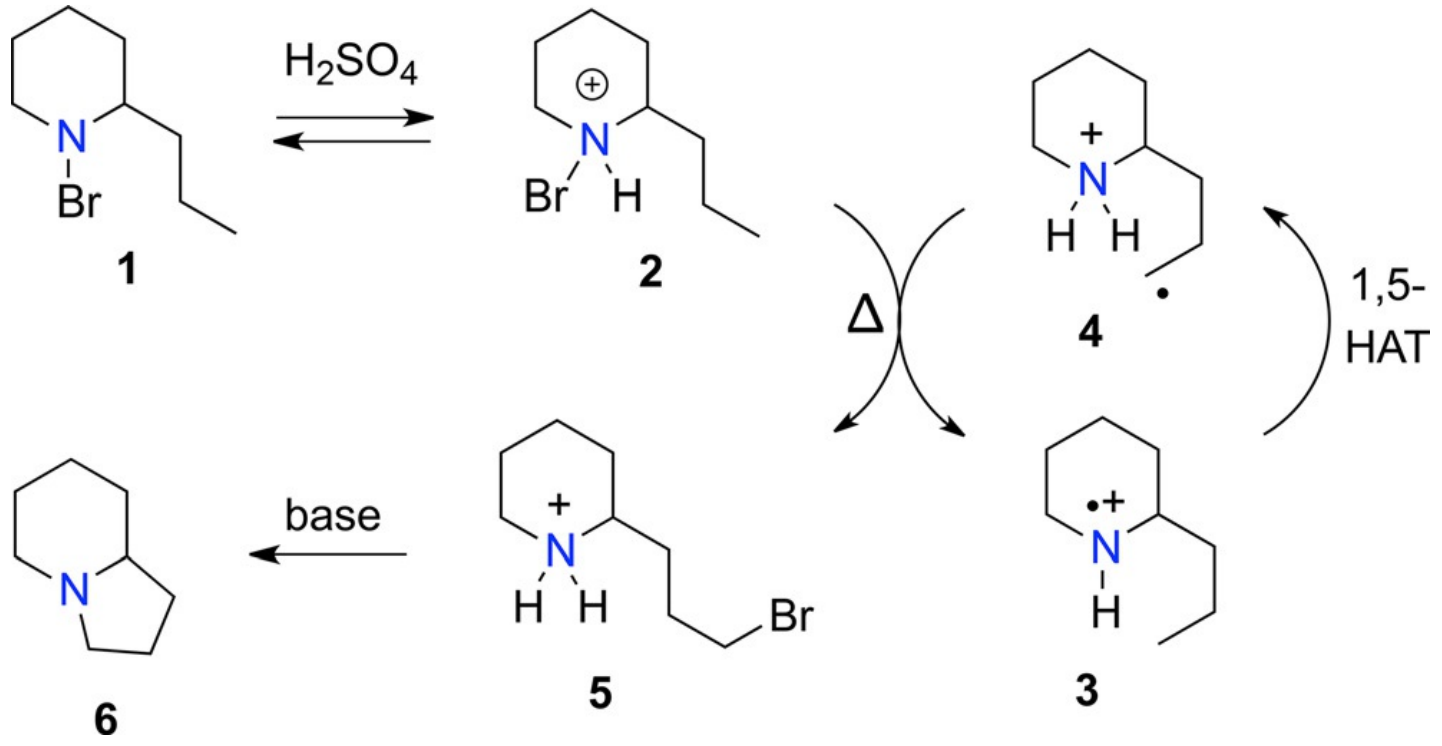
In vorliegender Arbeit sollte die in der vorangehenden Arbeit mit Erfolg durchgeführte Reaktion zur Bildung von Pyrrolidinderivaten auf das Dihydrometanicotin angewendet werden, wobei man dann im Sinne folgender Gleichung Nicotin erwarten konnte:



1909.

A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1883**, *16*(1), 558–560
K. Löffler, C. Freytag, *Ber. Dtsch. Chem. Ges.*, **1909**, *42*(3), 3427–3431
K. Löffler, S. Kober, *Ber. Dtsch. Chem. Ges.*, **1909**, *42*(3), 3431–3438

Hofmann-Löffler–Freytag



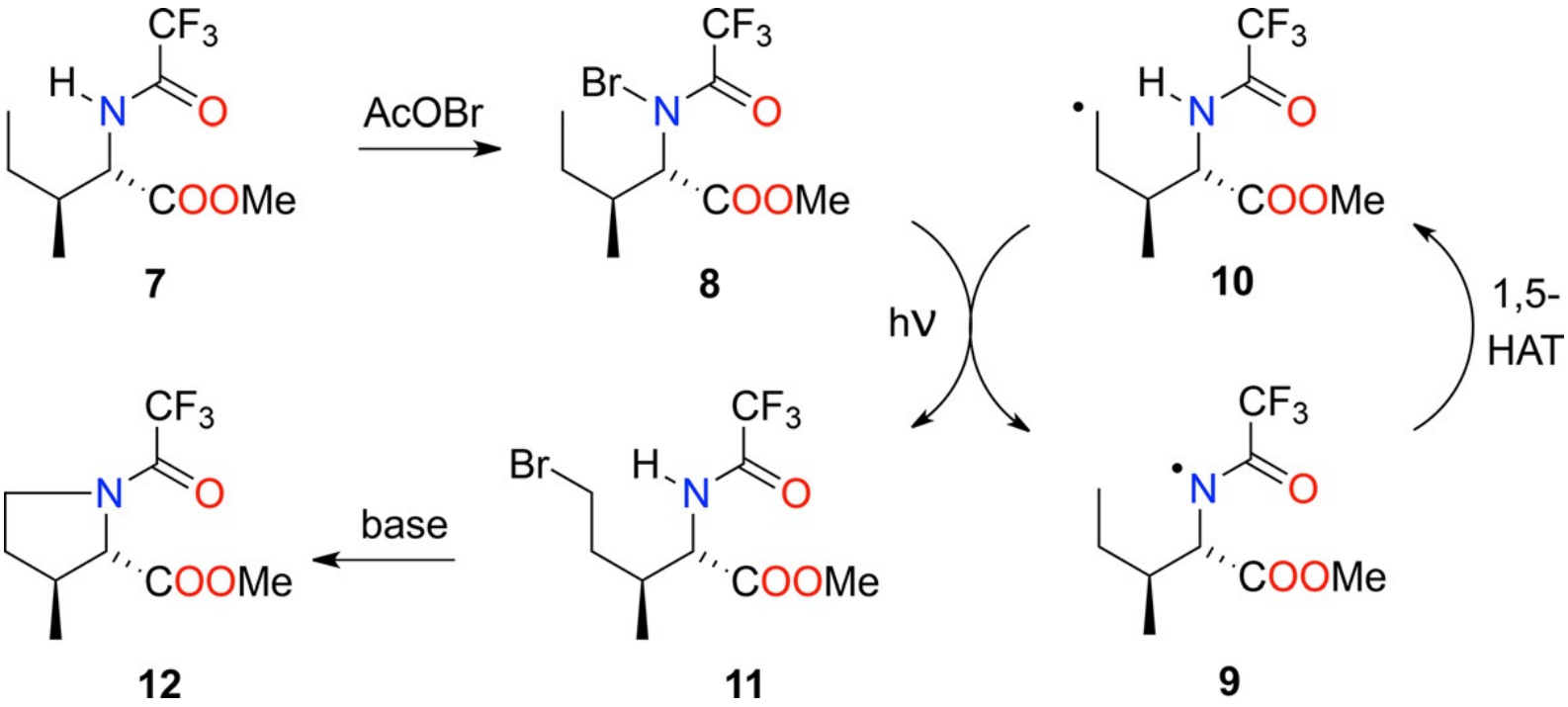
ESOR2023
Amsterdam

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*

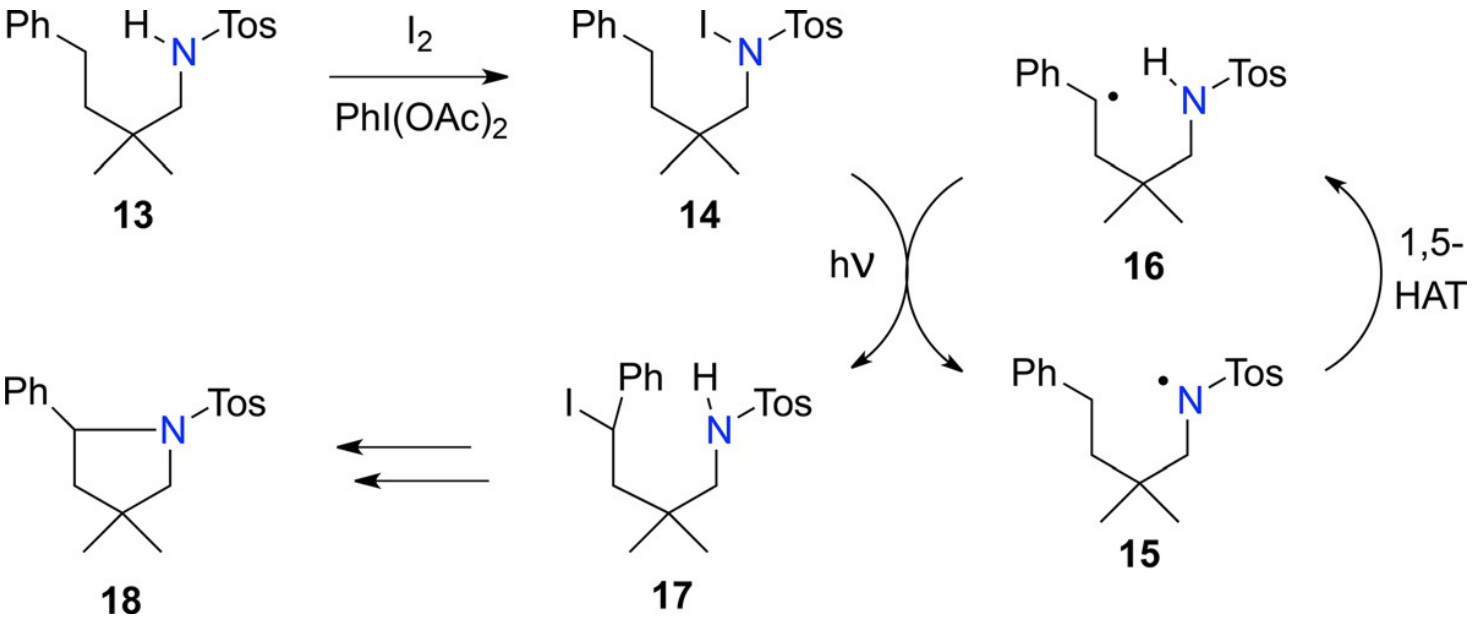


SYNTHESIS OF 1,4-EPIMINE COMPOUNDS. IODOSOBENZENE DIACETATE, AN EFFICIENT REAGENT FOR NEUTRAL NITROGEN RADICAL GENERATION

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**

Regioselectivity

Organic LETTERS

Letter

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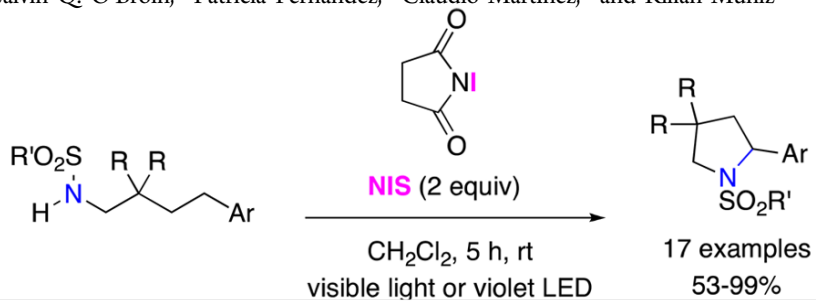
N-Iodosuccinimide-Promoted Hofmann–Löffler Reactions of Sulfonimides under Visible Light

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



OL | Organic Letters

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

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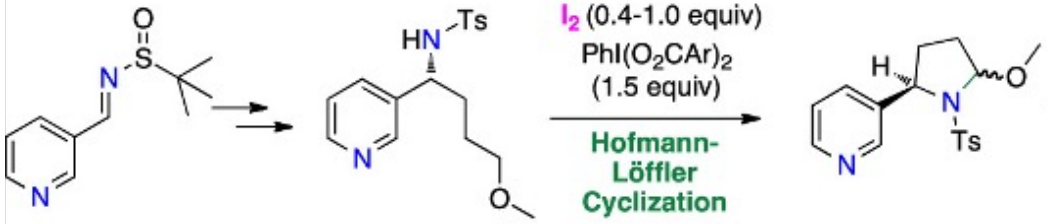
Enantioselective Synthesis of Nicotine via an Iodine-Mediated Hofmann–Löffler Reaction

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



Synthetic Methods

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

*Claudio Martínez and Kilian Muñiz**

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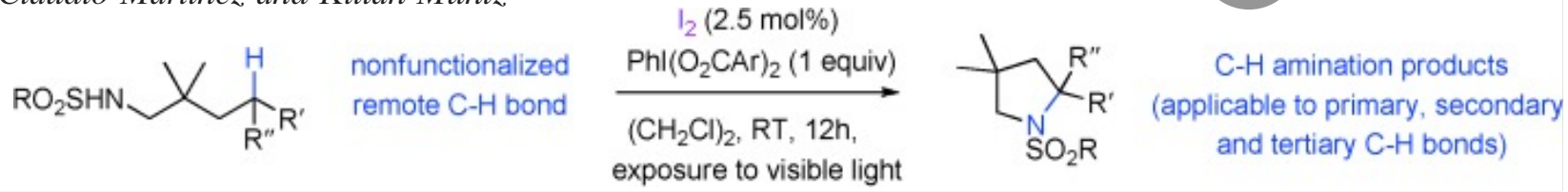

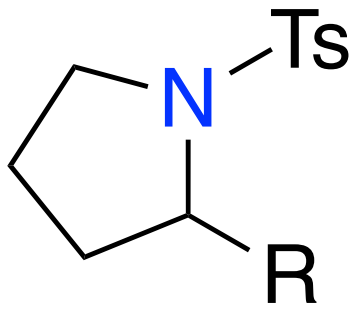

Regioselectivity

Chemical Science

ROYAL SOCIETY OF CHEMISTRY

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Cite this: *Chem. Sci.*, 2019, **10**, 2693

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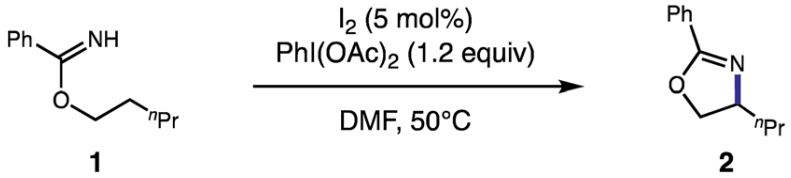
Catalytic β C–H amination *via* an imidate radical relay†

Leah M. Stateman, Ethan A. Wappes, Kohki M. Nakafuku, Kara M. Edwards and David A. Nagib *



1 2

Chemical Science

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Cite this: *Chem. Sci.*, 2019, **10**, 6915

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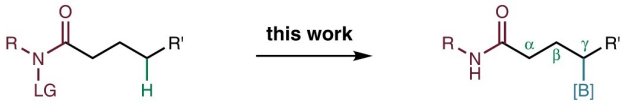
Practical, metal-free remote heteroarylation of amides *via* unactivated C(sp^3)–H bond functionalization†

Nana Tang,‡[a] Xinxin Wu‡[a] and Chen Zhu *[ab]

communications chemistry

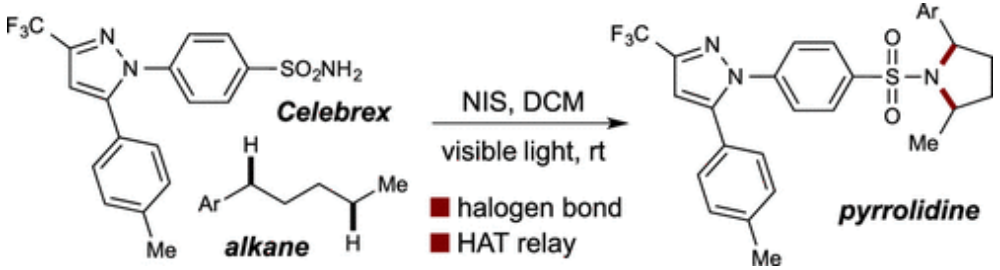
ARTICLE

https://doi.org/10.1038/s42004-023-00960-z



Transition metal-free visible light photoredox-catalyzed remote C(sp^3)–H borylation enabled by 1,5-hydrogen atom transfer

Beiqi Sun[1,2], Wenke Li[2], Qianyi Liu[2], Gaoge Zhang[2] & Fanyang Mo[1]✉



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Letter

Halogen-Bond-Induced Consecutive $C_{sp}{}^3$–H Aminations via Hydrogen Atom Transfer Relay Strategy

Fan Wu, Jeewani P. Ariyarathna, Navdeep Kaur, Nur-E Alom, Maureen L. Kennell, Omar H. Bassiouni, and Wei Li*

Regioselectivity?

ACS Catalysis

Letter

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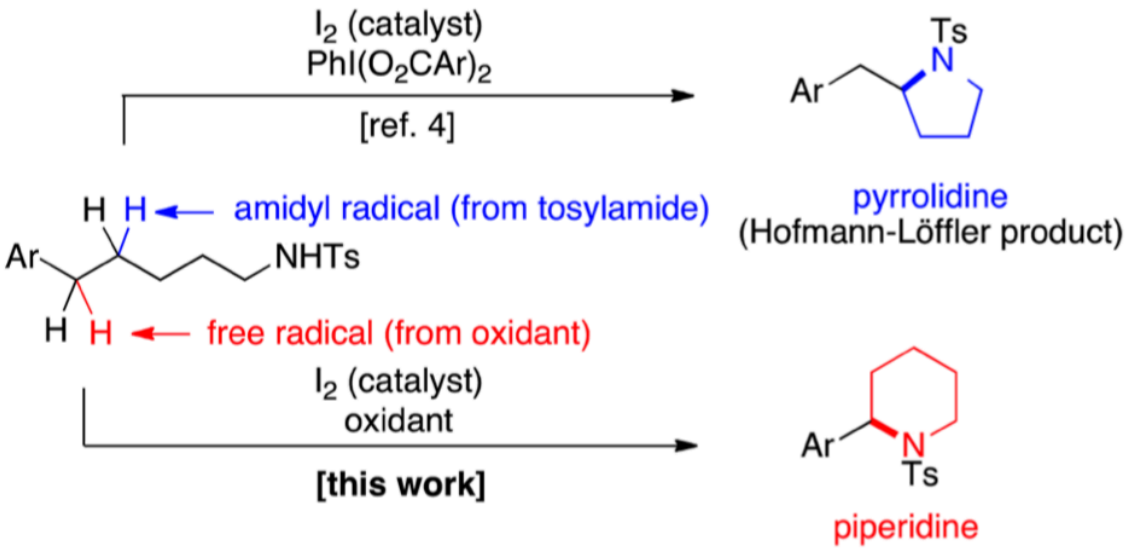
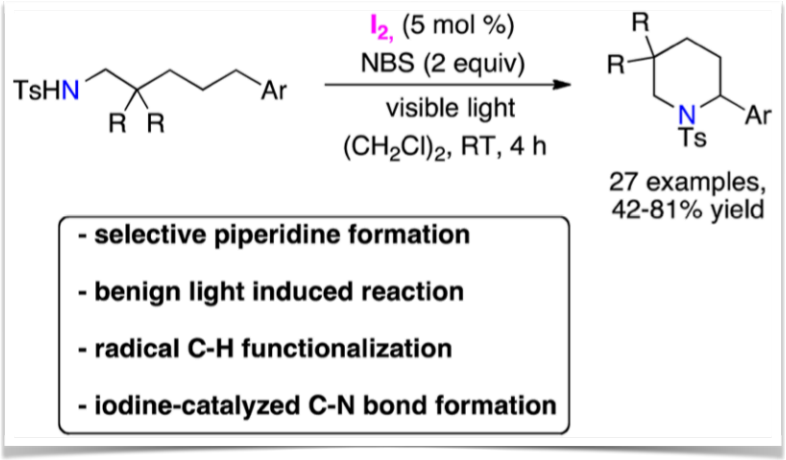
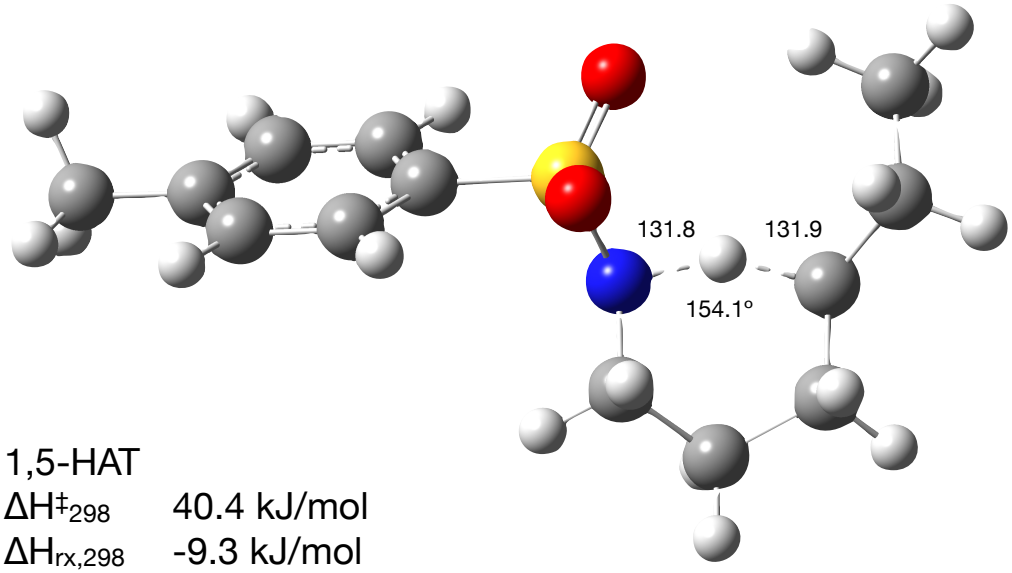
Selective Piperidine Synthesis Exploiting Iodine-Catalyzed C_{sp}^3–H Amination under Visible Light

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

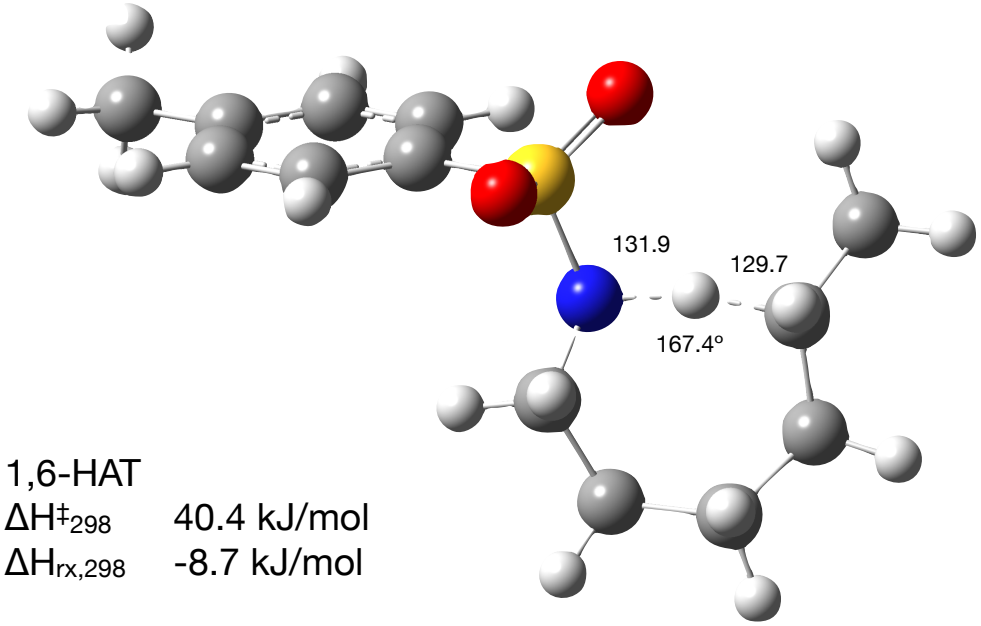




DFT will provide



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



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

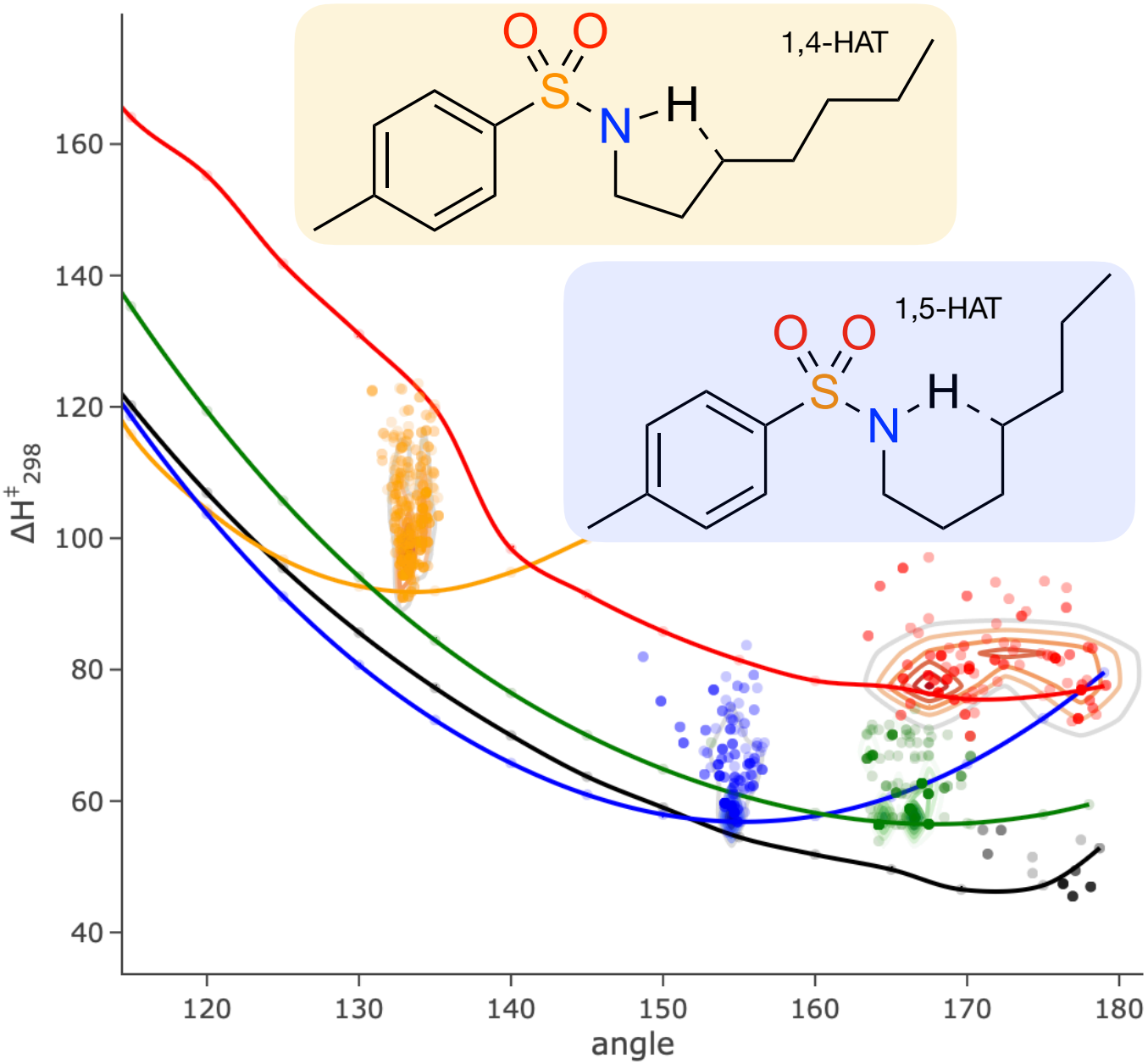
Difference: < 1kJ/mol

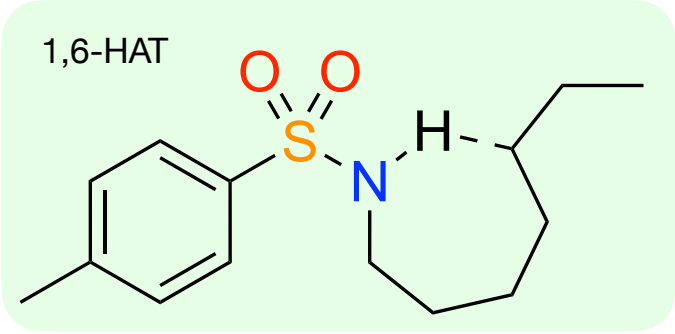
inside margin of error, QC accuracy

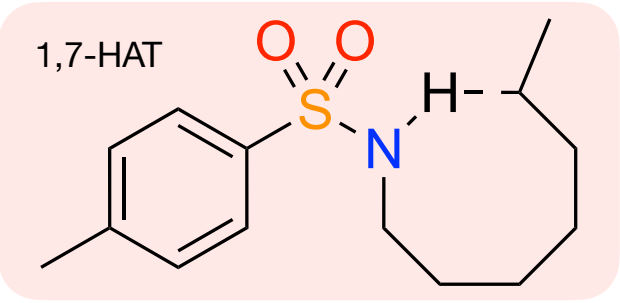
Theory: ~50%
Exp: >90%

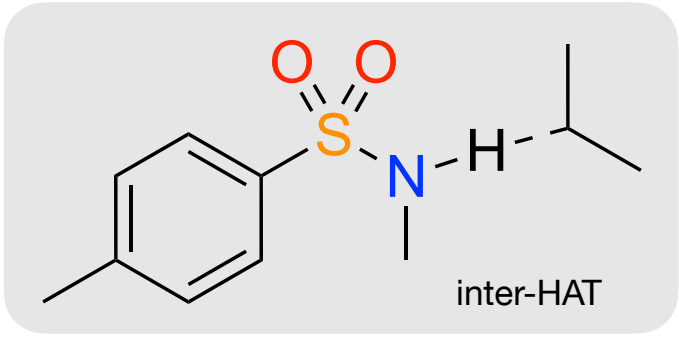
Theory: ~50%
Exp: trace

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

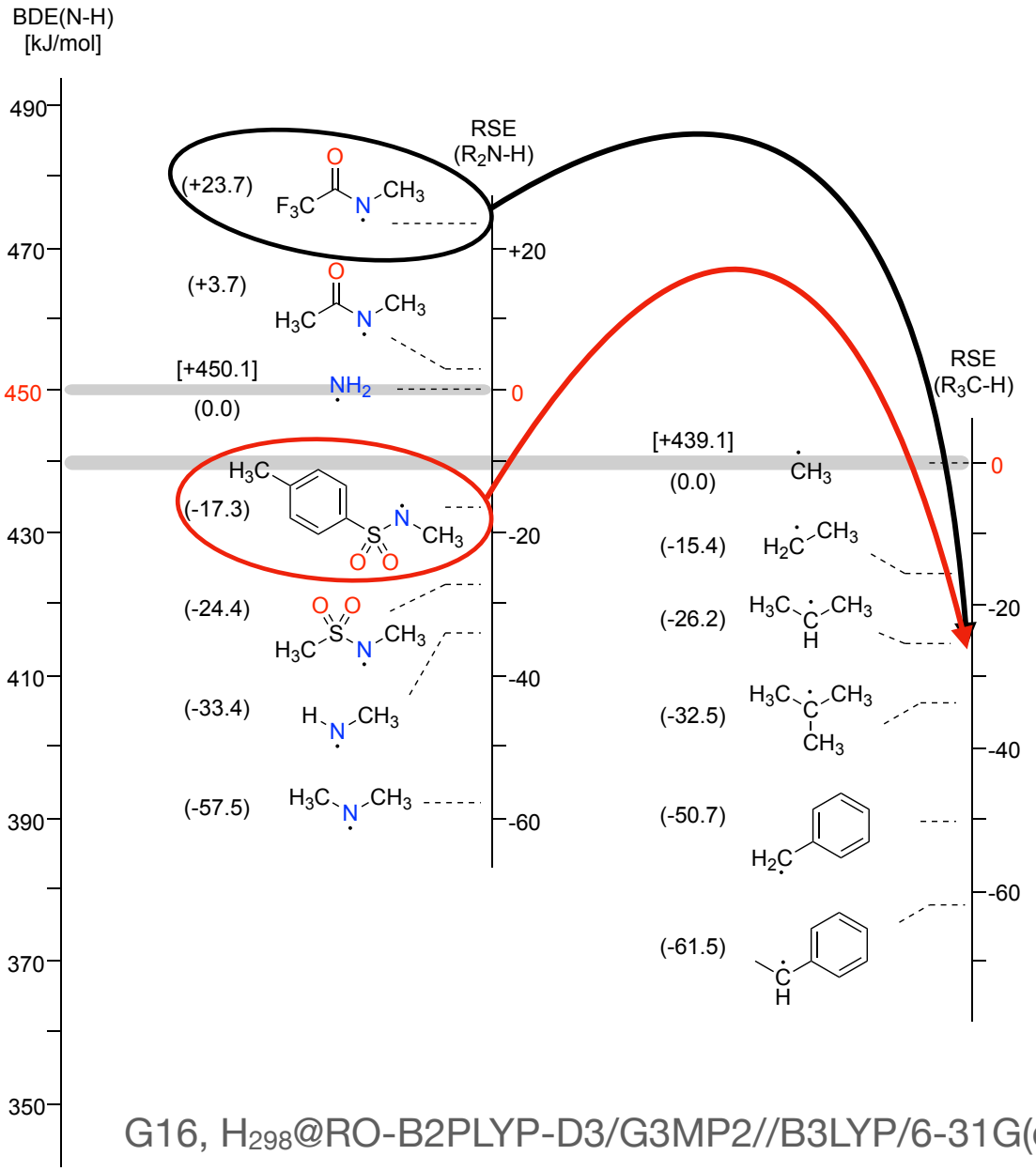




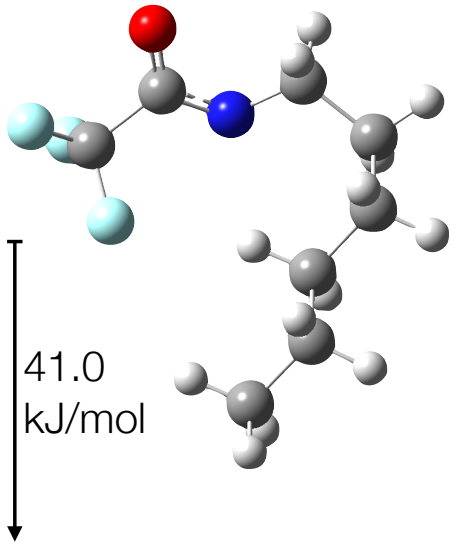




G16, H_{298}@B3LYP/6-31G(d)



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

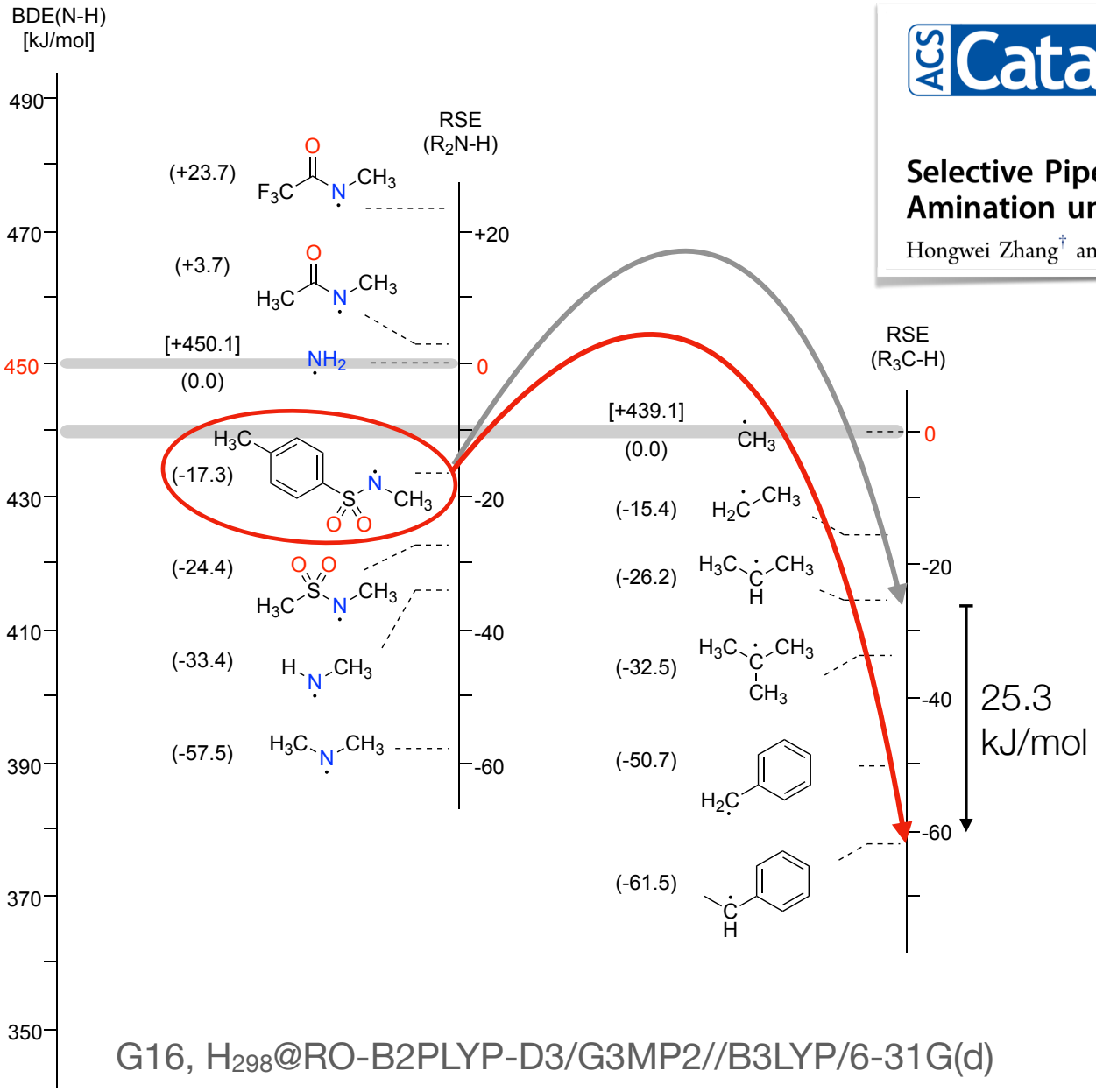
	$\Delta H^{\ddagger}_{298}$ kJ/mol	$\Delta H_{rx,298}$ kJ/mol
1,5-HAT	40.4	-9.3
1,6-HAT	40.4	-8.7

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}@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)

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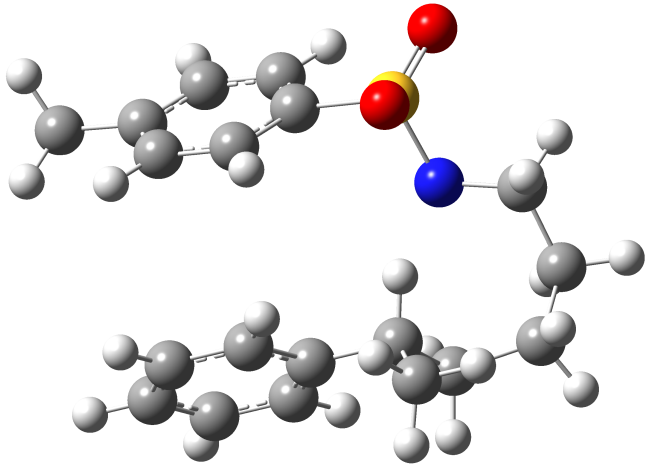
Selective Piperidine Synthesis Exploiting Iodine-Catalyzed C_{sp}^3–H Amination under Visible Light

Hongwei Zhang† and Kilian Muñiz*,†,‡

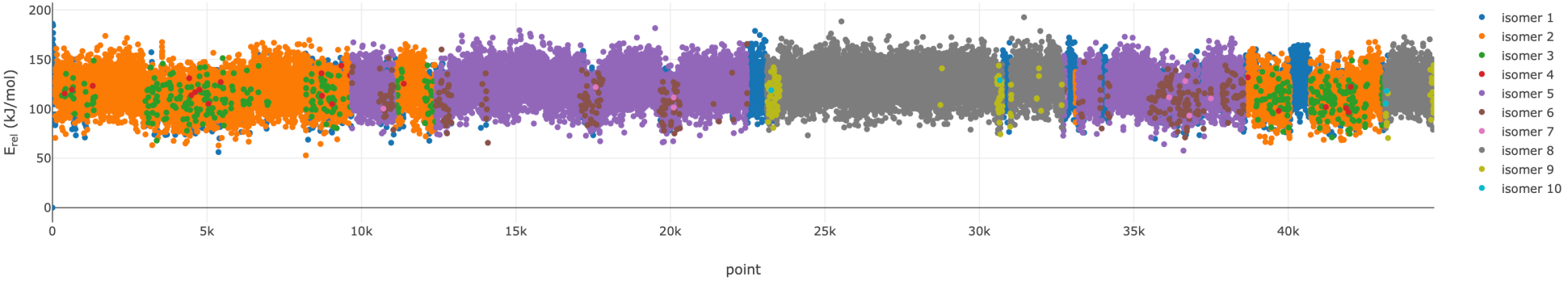


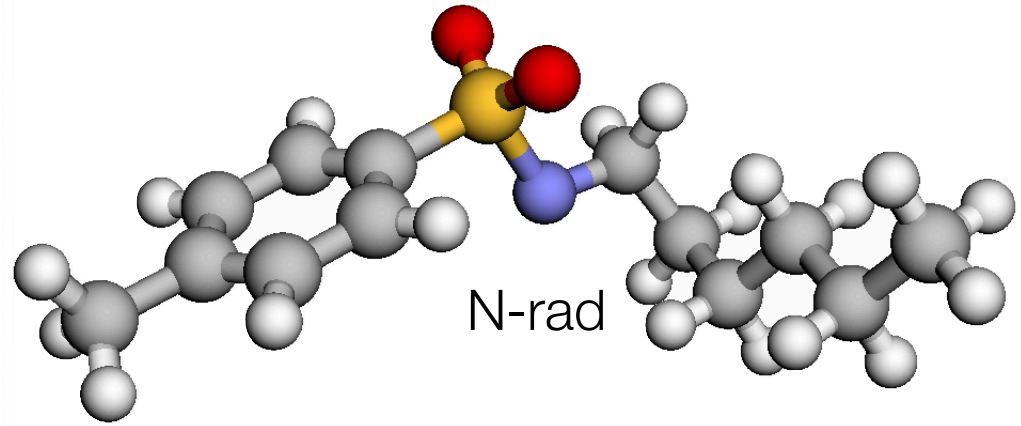
***N*-tosyl-(5-phenyl)hexylamine**

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

Can MD help?

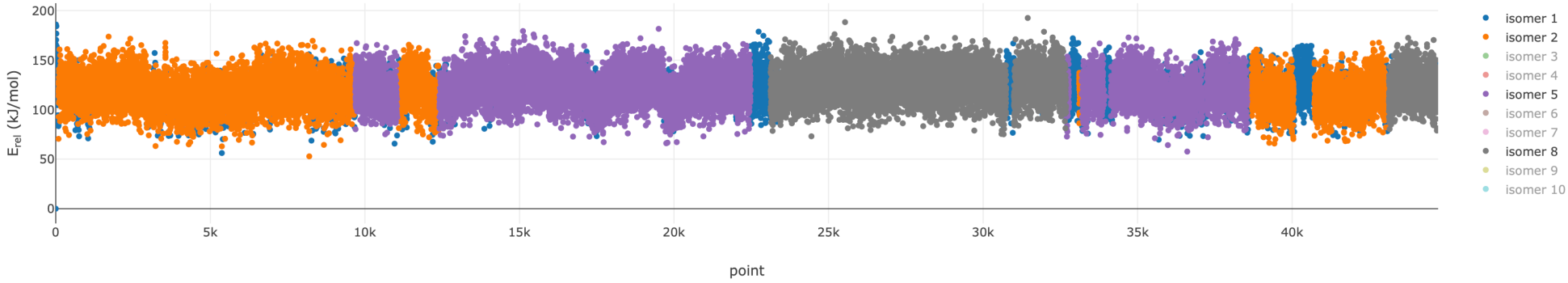
MD@xtb/GFN2, SHAKE=0, HMASS=2, TEMP=298.15K

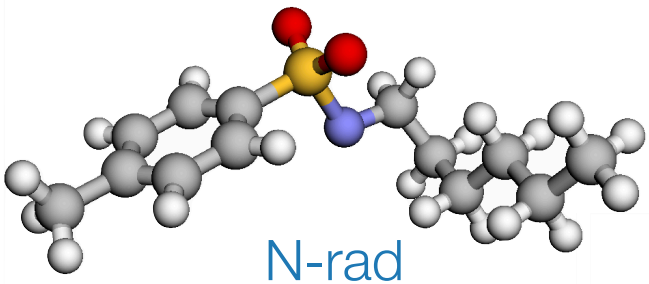




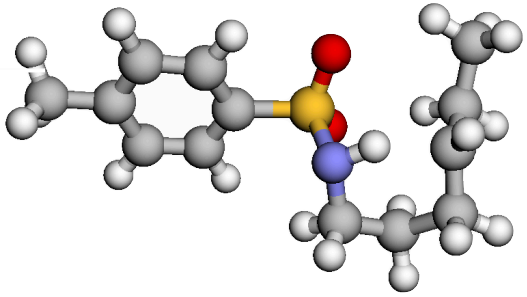
TrajectSCAN with Plotly & 3Dmol.js - to be published

No luck…

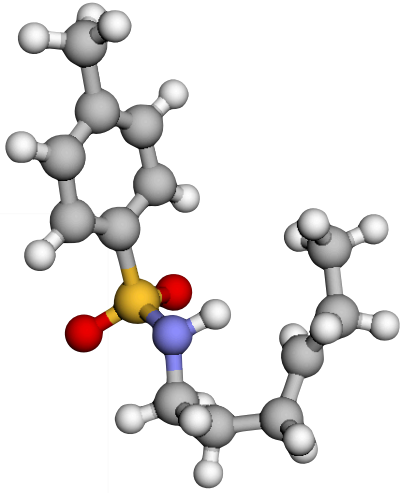




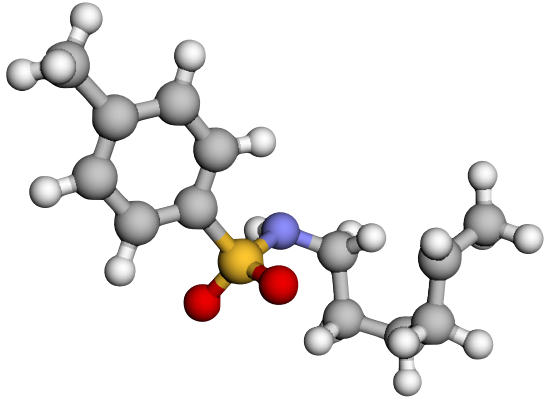
N-rad



C_5-rad



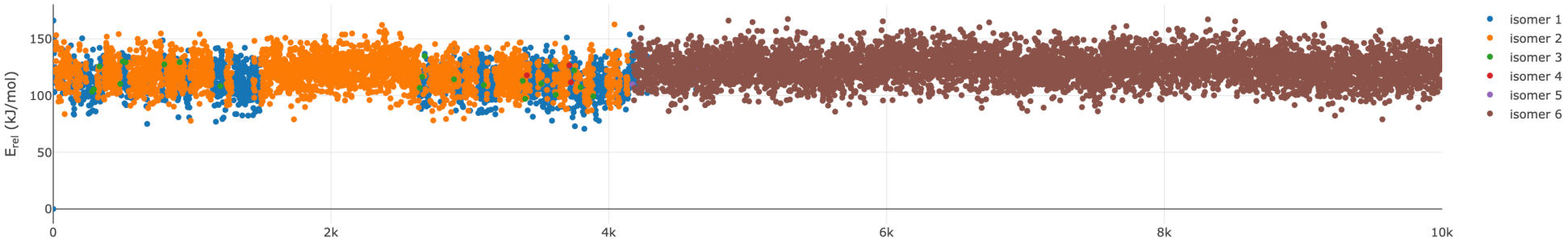
C_5-rad

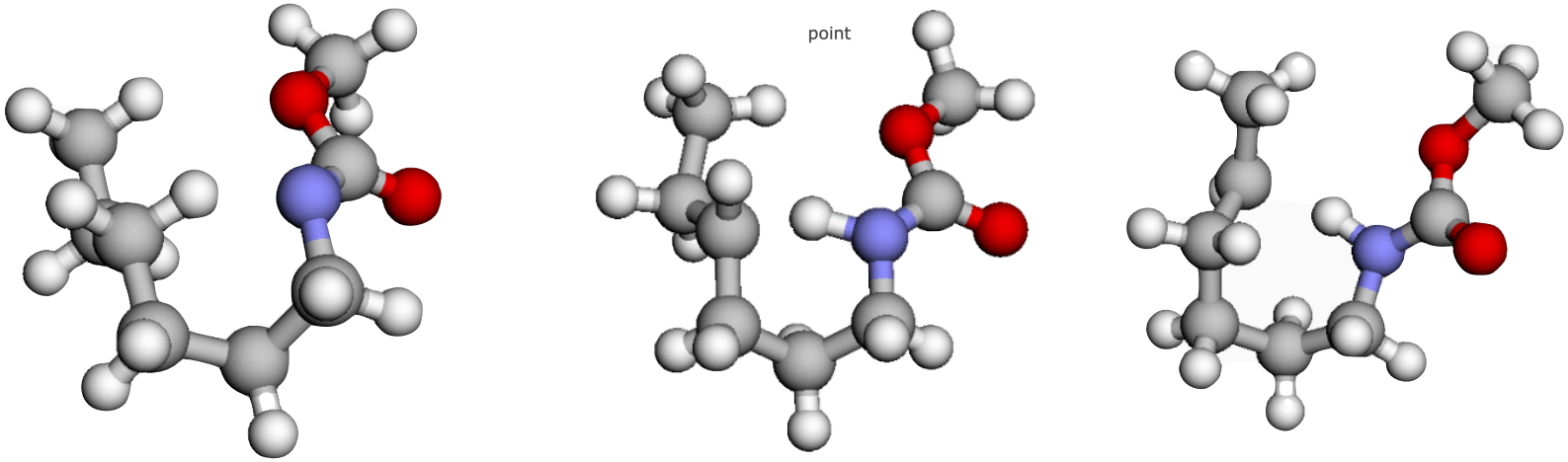


C_6-rad

MD for carbamates

MD@xtb/GFN2, SHAKE=0, HMASS=2, TEMP=298.15K





N-rad

C_5-rad

C_6-rad

MD

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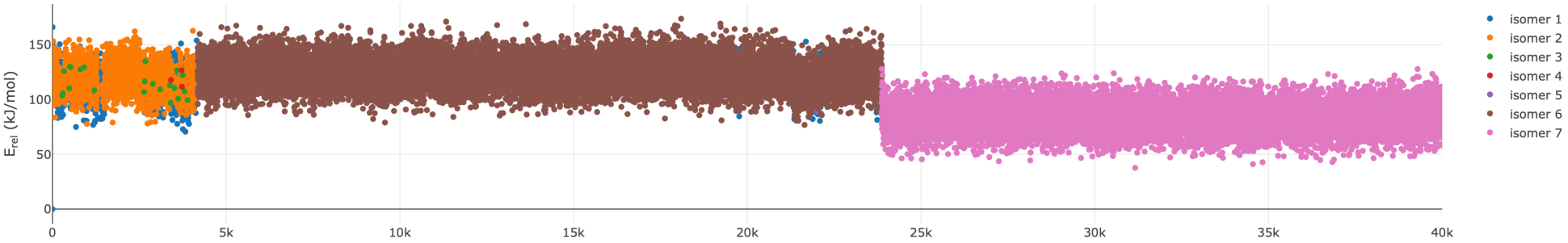
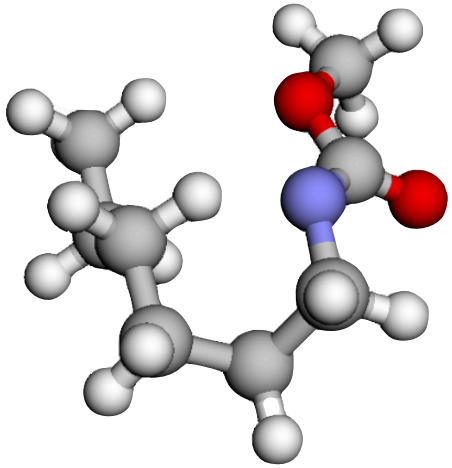
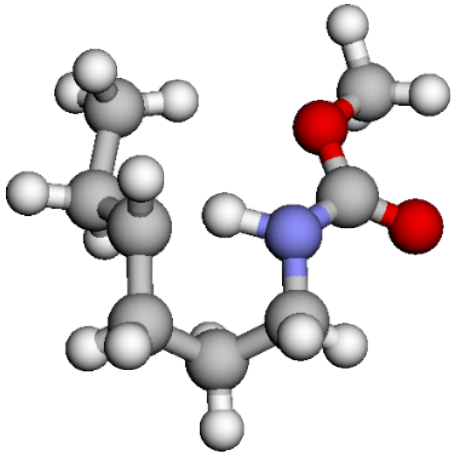
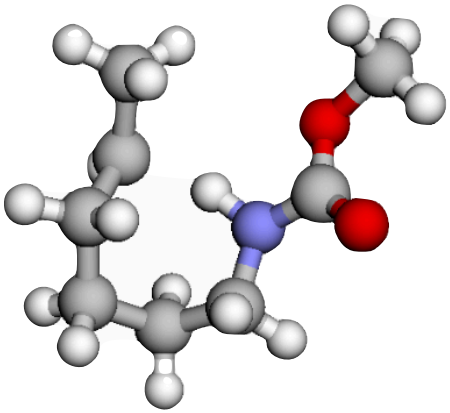




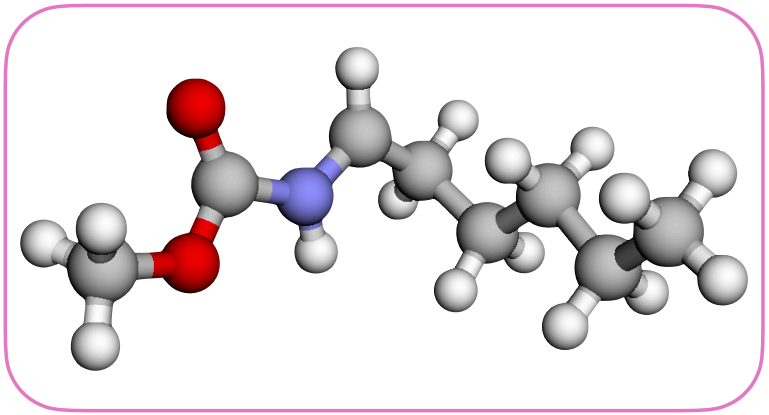
N-rad



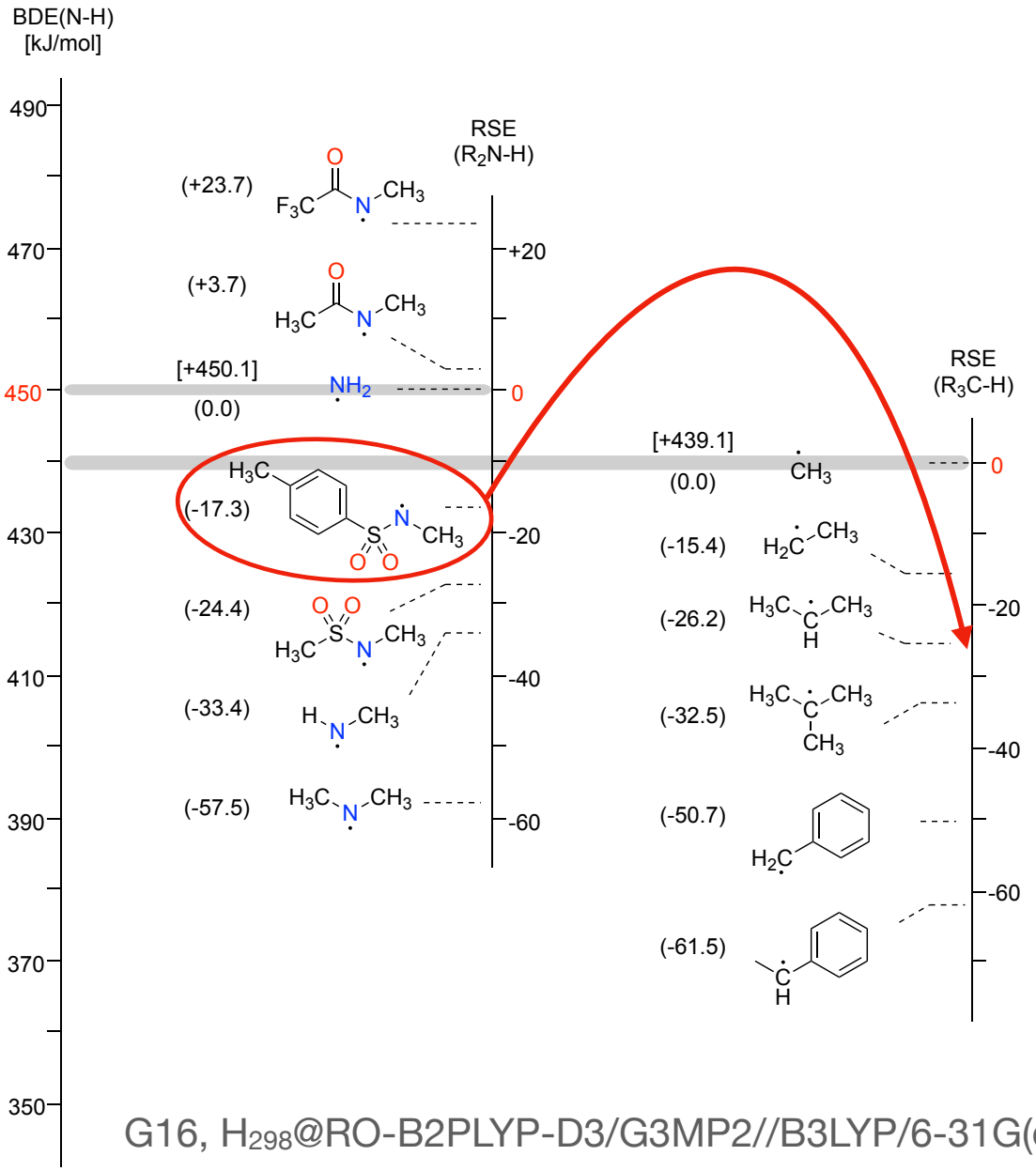
C_5-rad



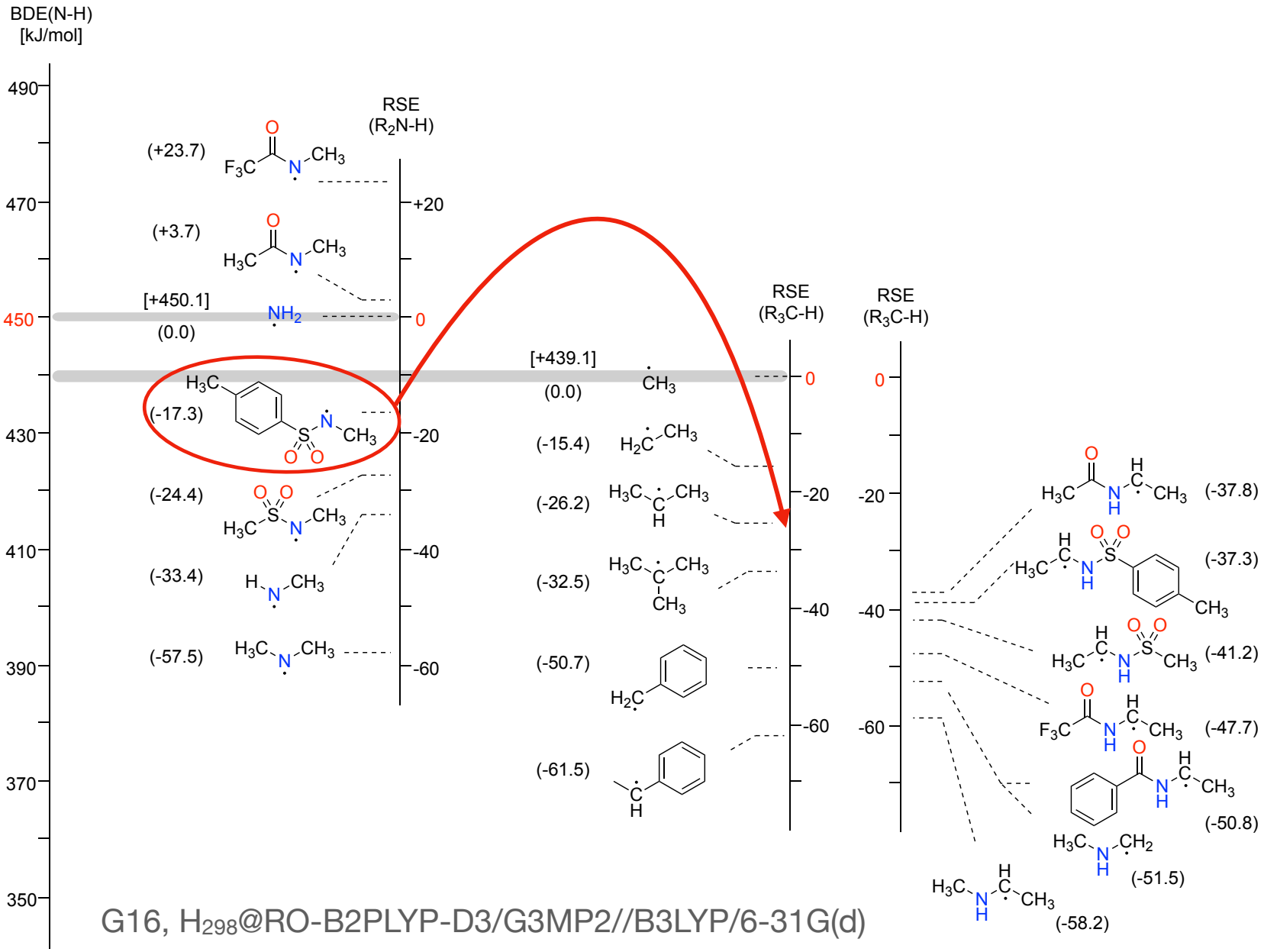
C_6-rad

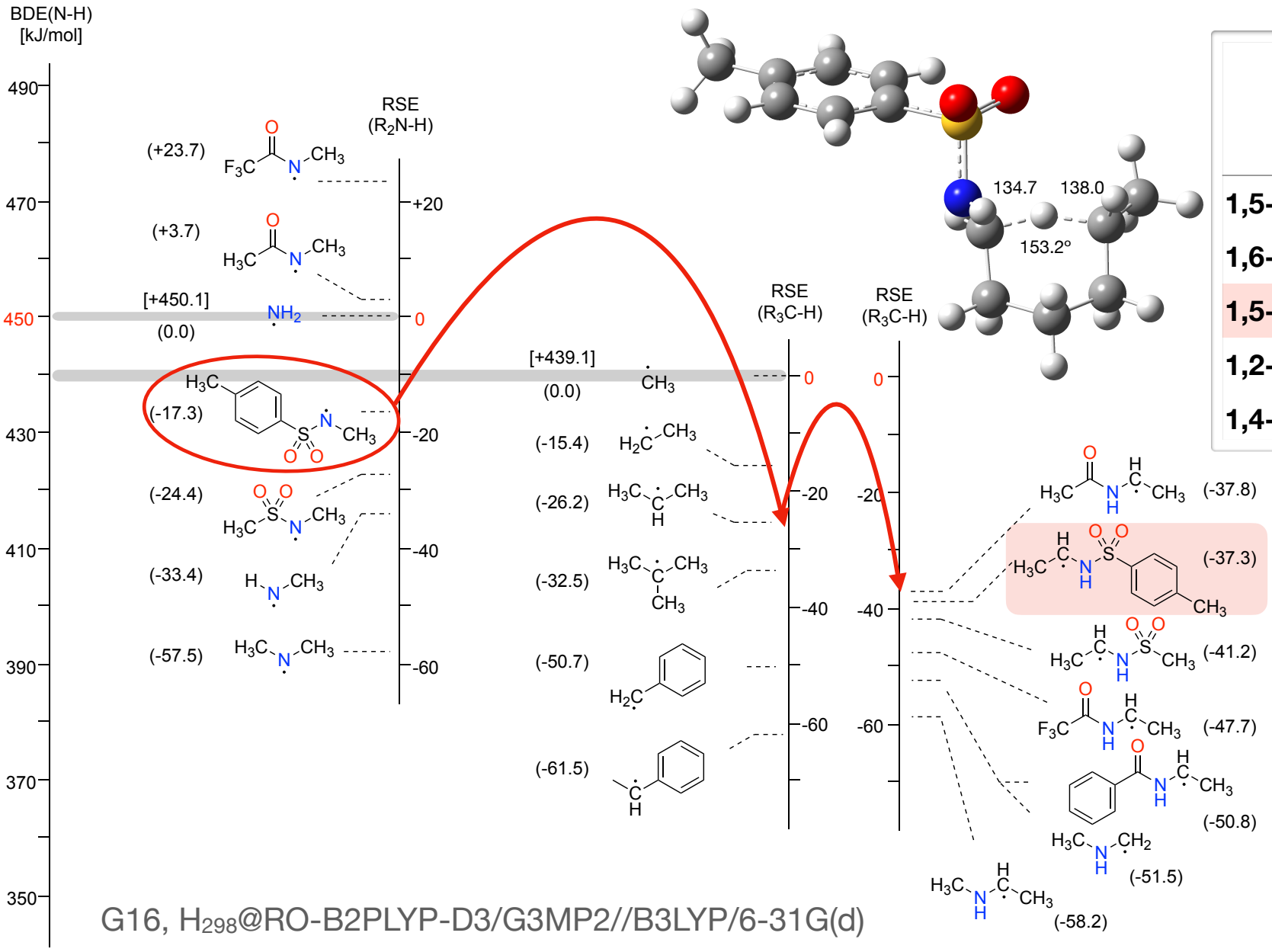


C_2-rad



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

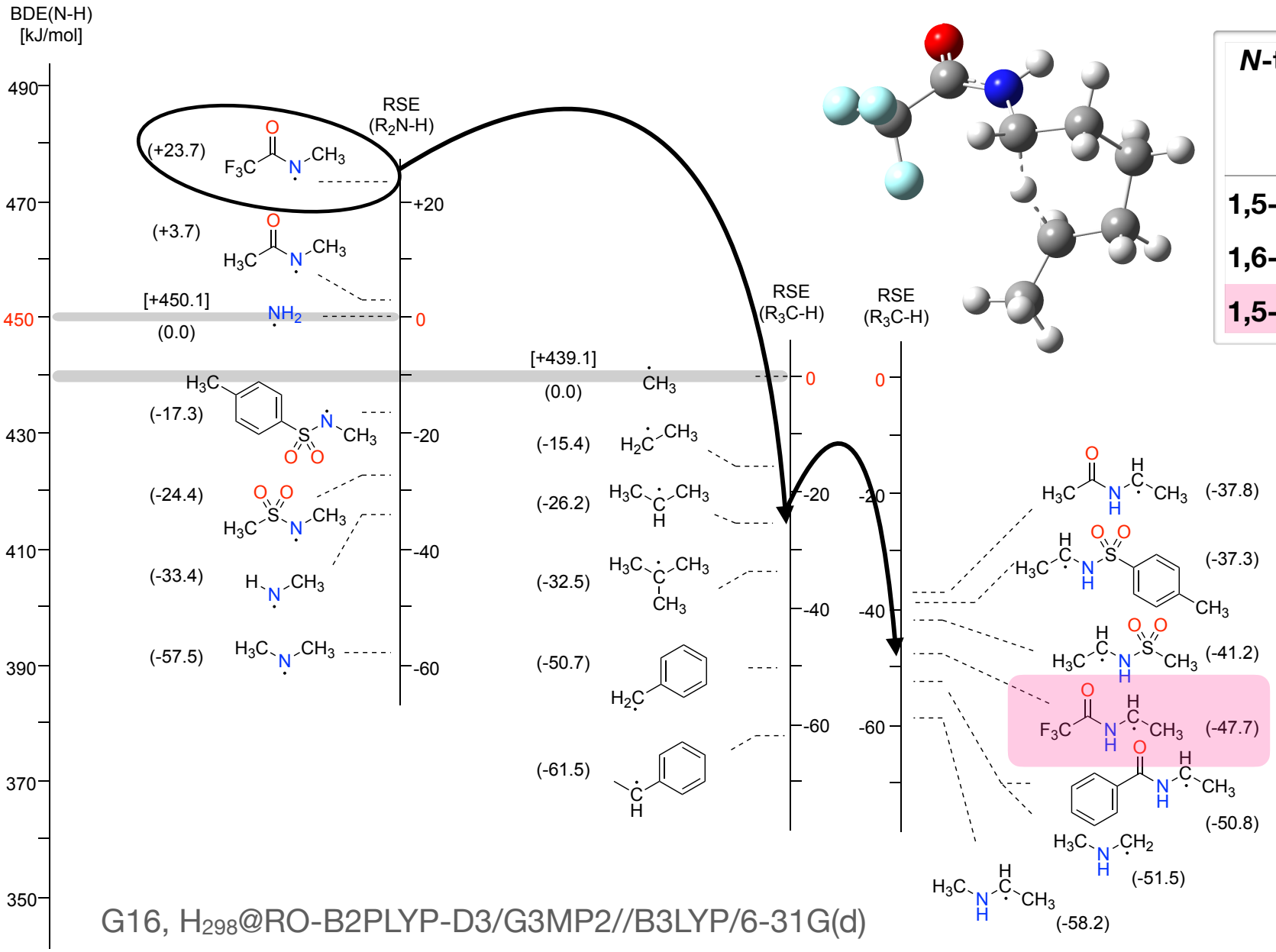

BDE(N-H)
[kJ/mol]
490
470
450
430
410
390
370
350
RSE
(R2N-H)
+20
0
-20
-40
-60
(+23.7)
(+3.7)
[+450.1]
(0.0)
(-17.3)
(-24.4)
(-33.4)
(-57.5)
RSE
(R3C-H)
[+439.1]
(0.0)
(-15.4)
(-26.2)
(-32.5)
(-50.7)
(-61.5)
RSE
(R3C-H)
(-37.8)
(-37.3)
(-41.2)
(-47.7)
(-50.8)
(-51.5)
(-58.2)
G16, H298@RO-B2PLYP-D3/G3MP2//B3LYP/6-31G(d)



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

***N*-tosyl-hexylamine**

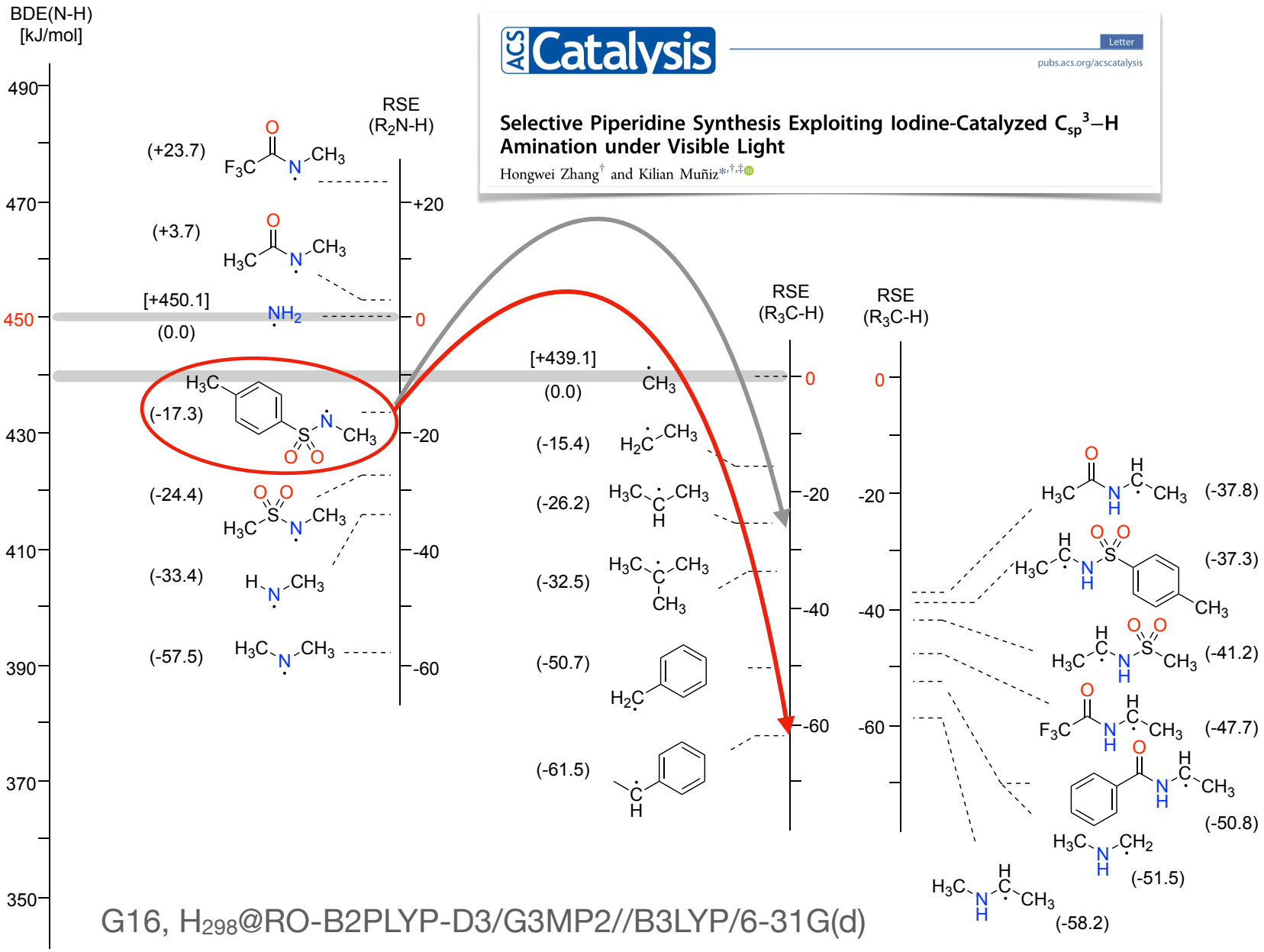
	$\Delta H^{\ddagger}_{298}$ kJ/mol	$\Delta H_{rx,298}$ kJ/mol
1,5-HAT$_{NC}$	40.4	-9.3
1,6-HAT$_{NC}$	40.4	-8.7
1,5-HAT$_{CC}$	57.4	-22.5
1,2-HAT$_{NC}$	153.2	-20.3
1,4-HAT$_{CC}$	111.2	-21.9



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$_{NC}$	36.6	-37.9
1,6-HAT$_{NC}$	38.0	-30.3
1,5-HAT$_{CC}$	57.6	-15.5



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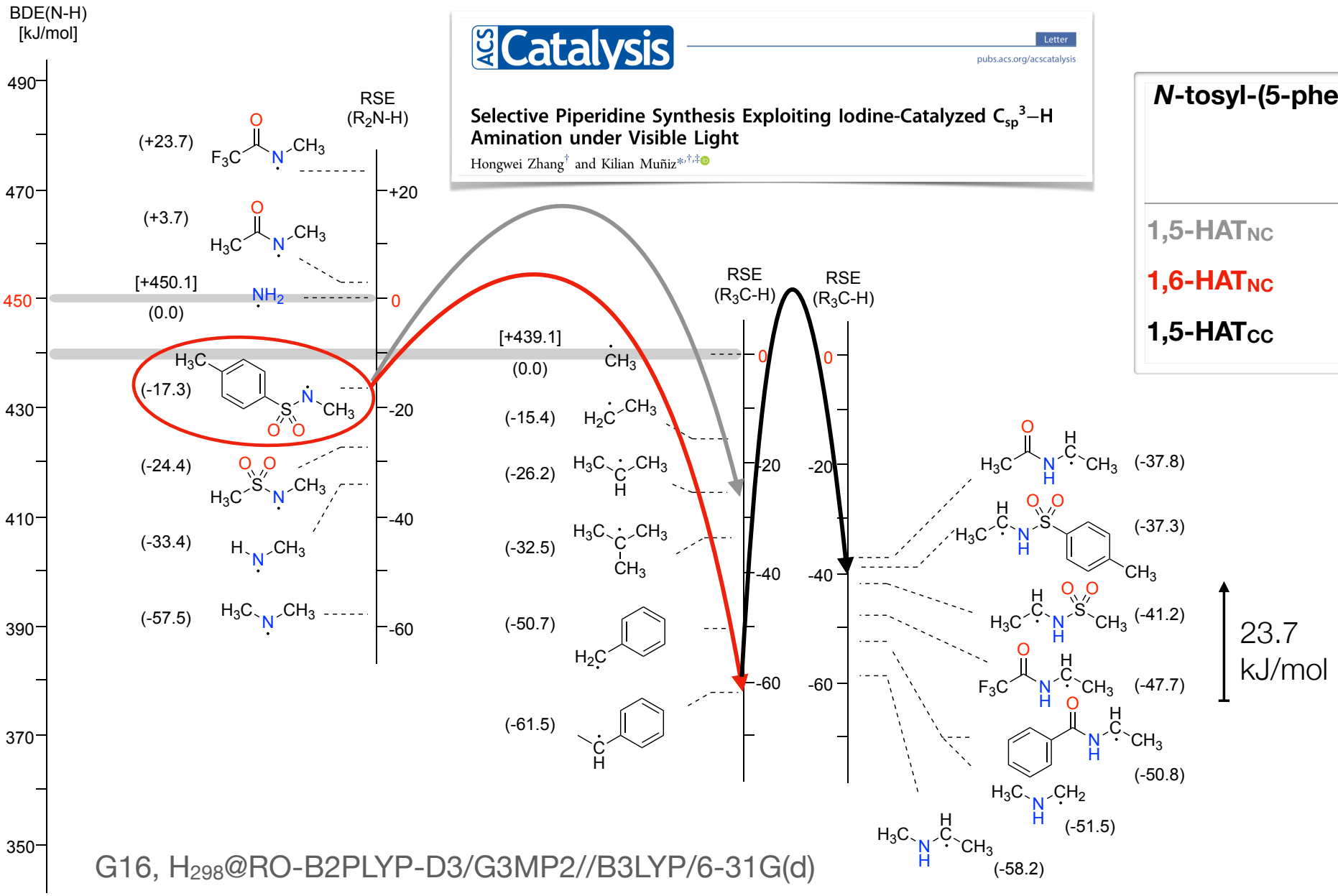
Selective Piperidine Synthesis Exploiting Iodine-Catalyzed $C_{sp}{}^3$–H Amination under Visible Light

Hongwei Zhang† and Kilian Muñiz*,†,‡

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



ACS Catalysis

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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

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

Chemistry
A European Journal

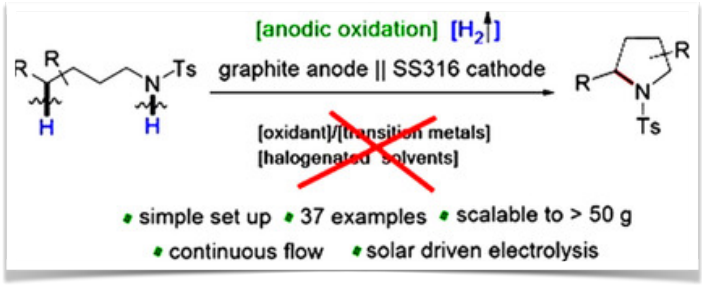
Chemistry Europe
European Chemical Societies Publishing

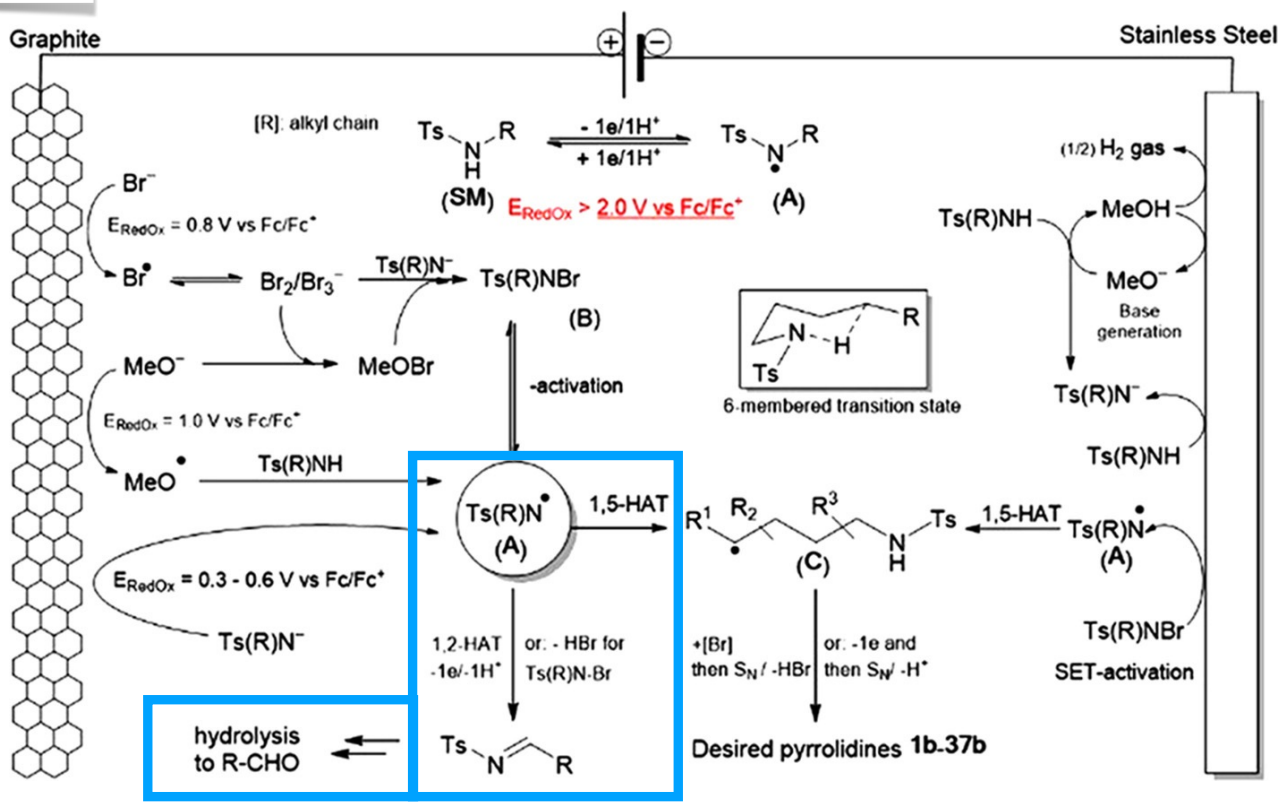
Full Paper

Electrochemical and Scalable Dehydrogenative C(sp^3)–H Amination via Remote Hydrogen Atom Transfer in Batch and Continuous Flow

Dr. Pavlo Nikolaienko, Marc Jentsch, Dr. Ajit P. Kale, Dr. Yunfei Cai, Prof. Dr. Magnus Rueping

First published: 12 March 2019 | https://doi.org/10.1002/chem.201806092 | Citations: 29





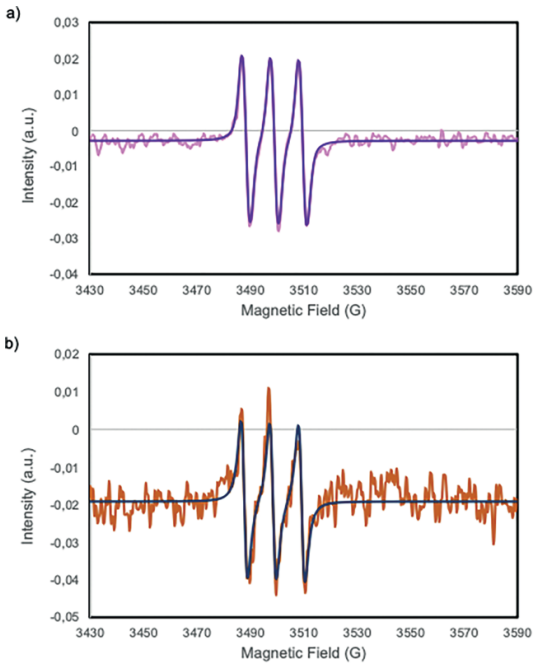
Experimental

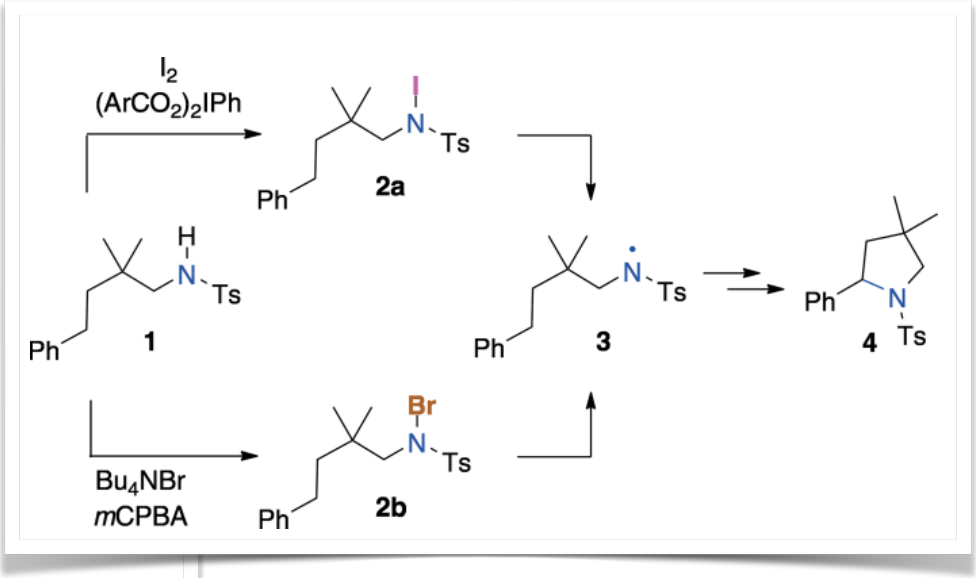
ChemPubSoc Europe
DOI: 10.1002/ejoc.201900497
EurJOC Communication

Amidyl Radical Intermediates | *Very Important Paper* |

VIP **Detection of the Elusive Nitrogen-Centered Radicals from Catalytic Hofmann–Löffler Reactions**

Alexandra E. Bosnidou,[a,b] Thomas Duhamel,[a,c] and Kilian Muñiz*[a,d]





EPR

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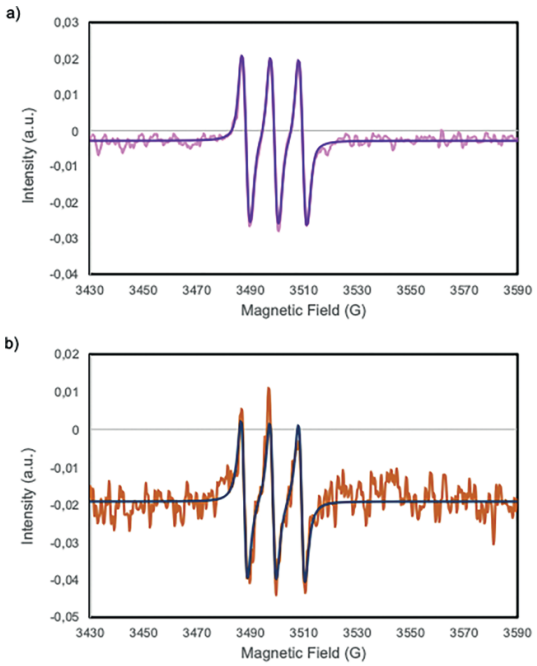
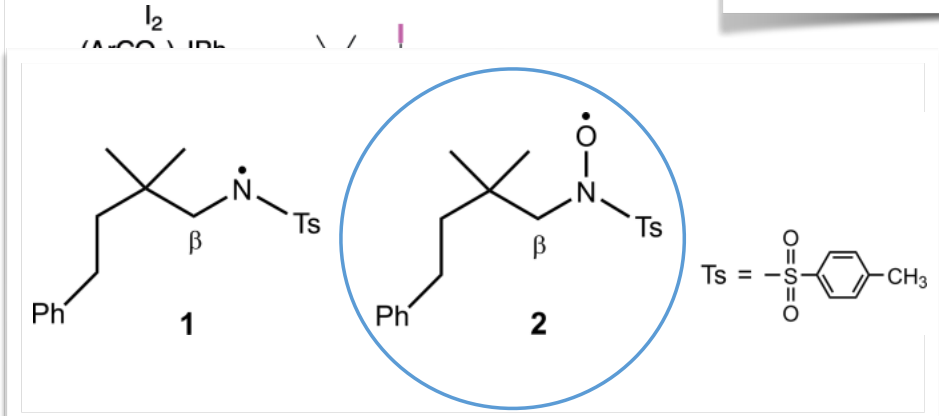
Detection of the Elusive Nitrogen-Centered Radicals from Catalytic Hofmann–Löffler Reactions

Alexandra E. Bosnidou,[a,b] Thomas Duhamel,[a,c] and Kilian Muñiz*[a,d]



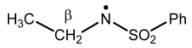
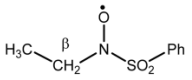
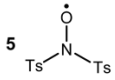
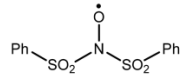
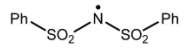


EurJOC European Journal of Organic Chemistry
CORRESPONDENCE
doi.org/10.1002/ejoc.201900922

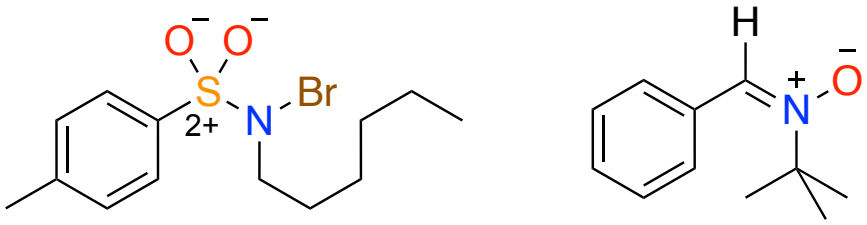
Amidyl Radical Intermediates

Comment on "Detection of the Elusive Nitrogen-Centered Radicals from Catalytic Hofmann–Löffler Reactions"

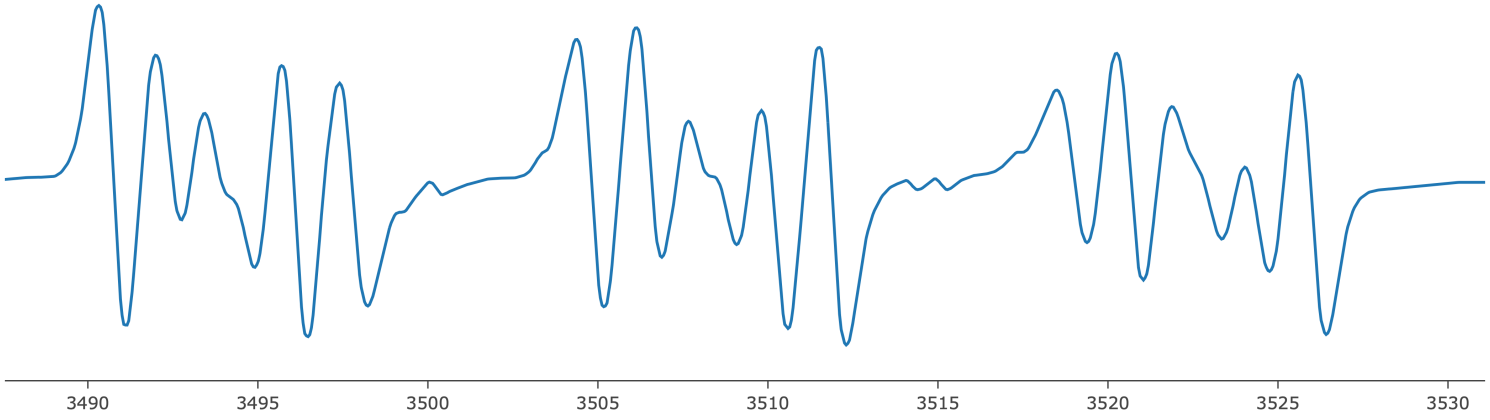
Hans-Gert Korth*[a]

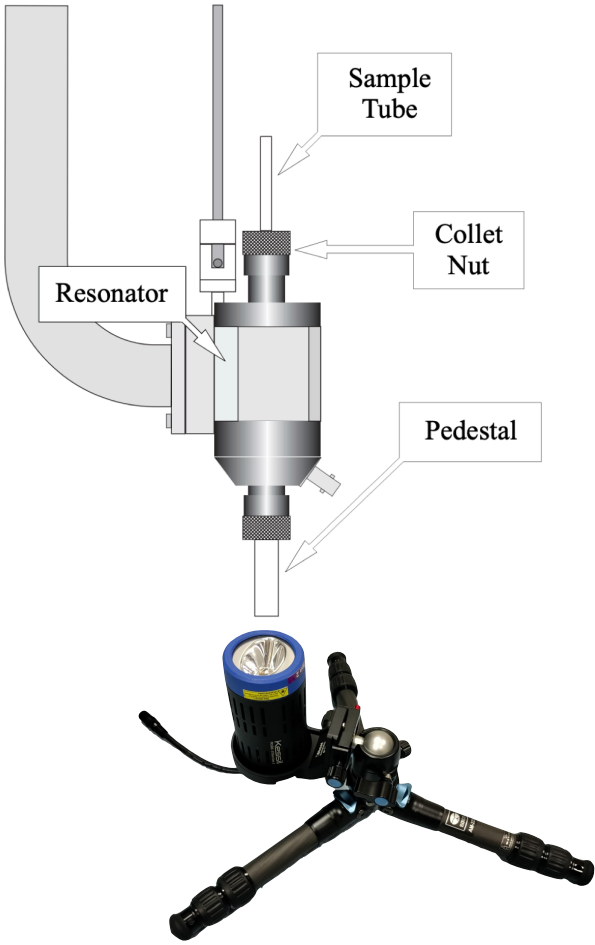
	Radical	*g*-Factor	Hyperfine Splittings [G] $a(^{14}N)$	$a(^{1}H_{\beta})$
3		2.0042	8.78	42.95 (2H)
4		2.0059	6.96	6.76 (2H)
5		2.0064[b] 2.0065[c]	10.50[b] 10.58[c]	
6		2.0050	8.87	
7		2.0041	7.83	

[a] DFT computations on the UB3LYP/CBSB7 level of theory employing the SMD solvation model for toluene solution. [b] Experimental data (in benzene) from ref.;[4] Ts = *para*-tolylsulfonyl. [c] Experimental data (in toluene) from Figure 4a and SI, p. S11, of ref.[1]



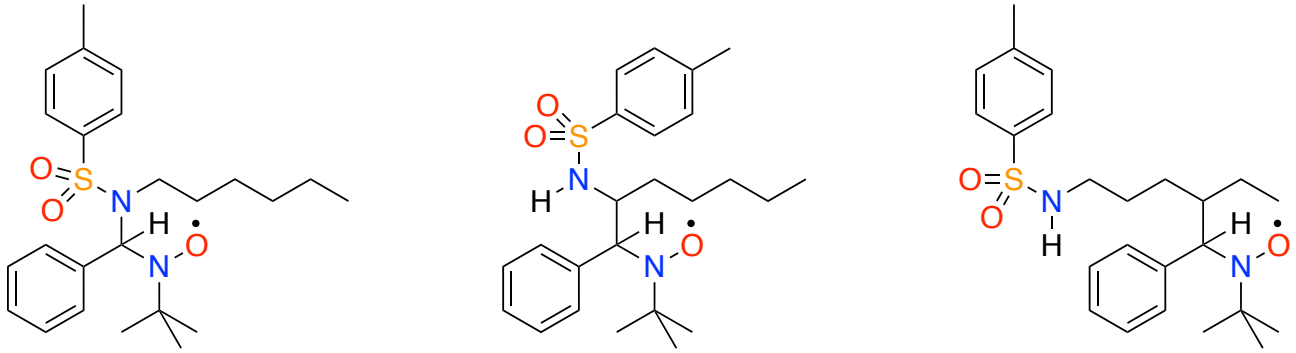
N-tert-butyl-α-phenylnitrone (PBN)

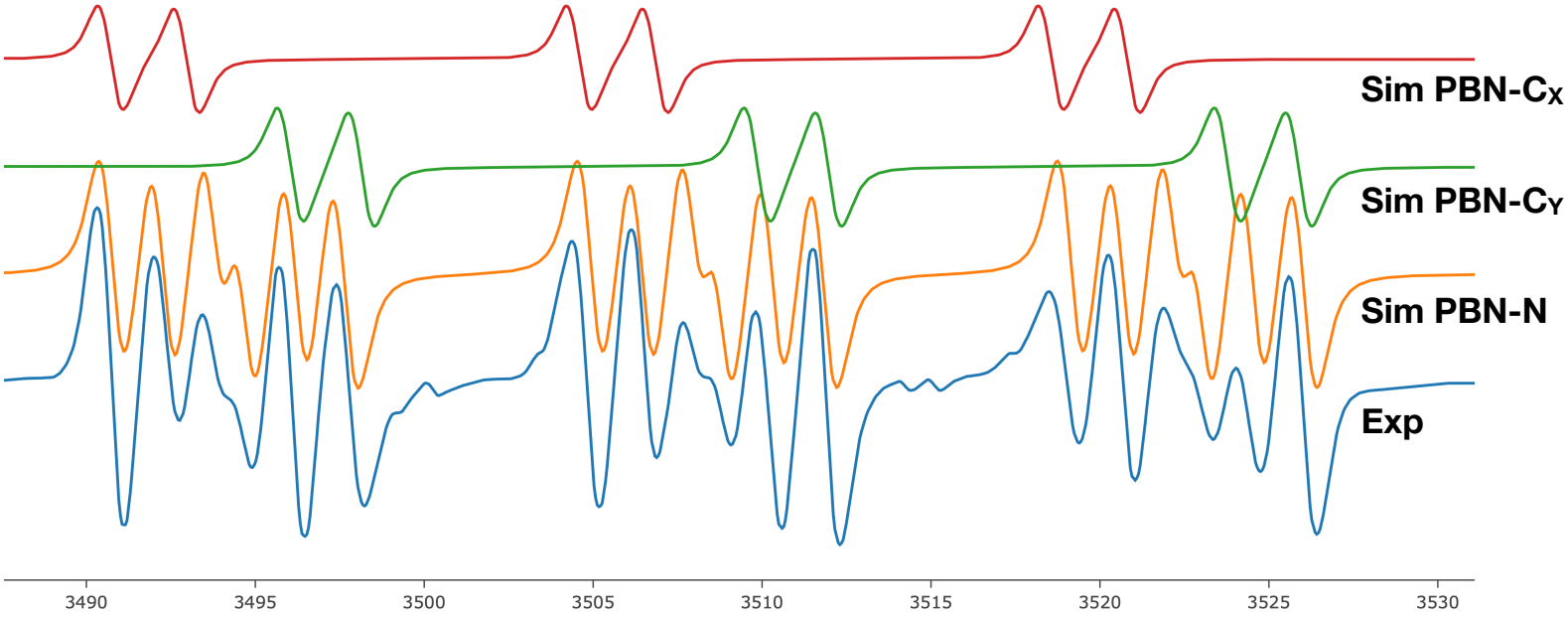


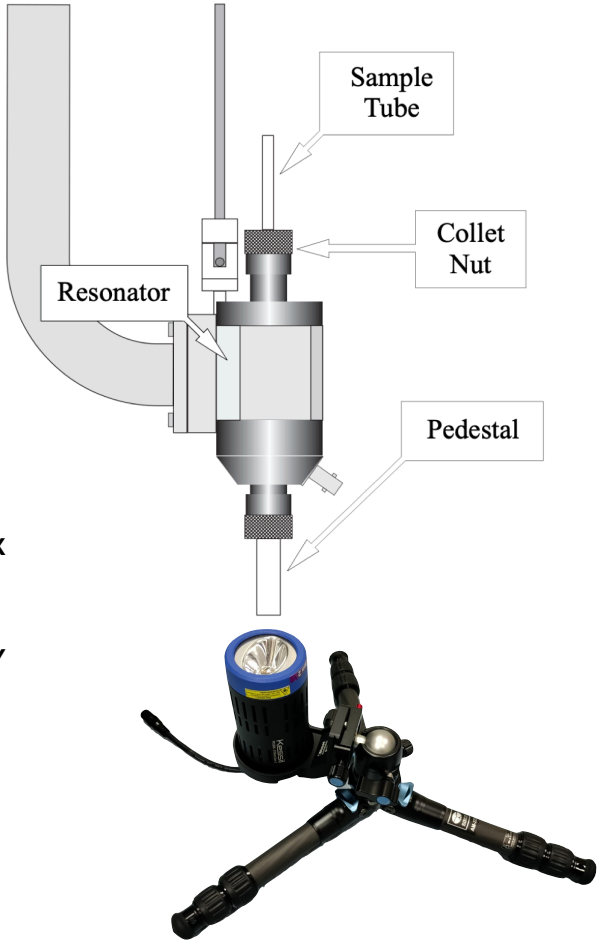


Kesil 370 nm Gen2

VisualEPR - to be published



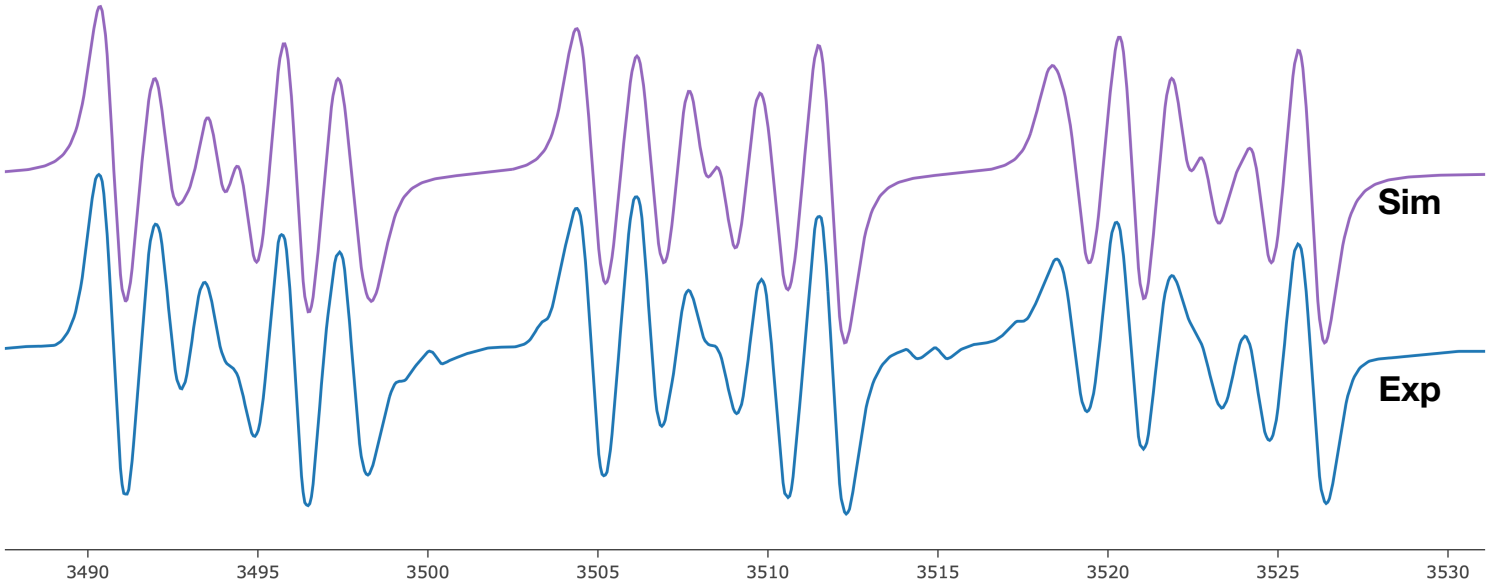


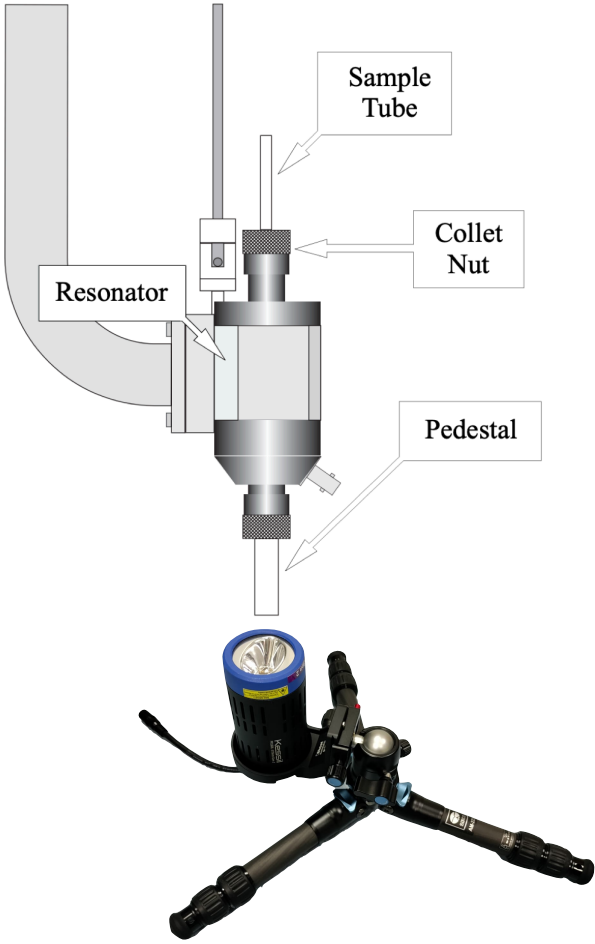


EasySpin MATLAB simulation

VisualEPR - to be published

	a_N	*hfc* $a_{N'}$	a_H	Ratio
PBN-N	14.24	1.52	3.90	1
PBN-C_X	13.91	-	2.11	0.17
PBN-C_Y	13.99	-	2.24	0.14





Conclusions

- Reaction is always more complicated then it seems
- Unexpected stable radicals are lurking around
- Sometimes MD at semi-empirical level gives more insight then DFT
- But only trust energies from DFT with well tested and proven method
- Interplay of theory and experiments

Valerije Vrček
Gabrijel Zubčić
Erim Bešić

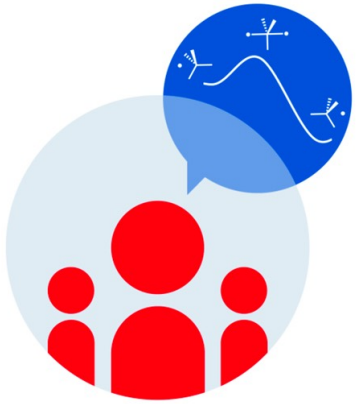
Jiangyang You
Tomislav Portada

Dean Marković
Maria Kolympadi Marković

Hendrik Zipse
Fabian Zott
Salavat Ashirbaev

Thank you!

ESOR2023
Amsterdam



Croatian Science Foundation