

**Svjetlošću pogonjena funkcionalizacija
nereaktivnih pozicija korištenjem
oksidacijske aminacije
(LIGHT-N-RING)**

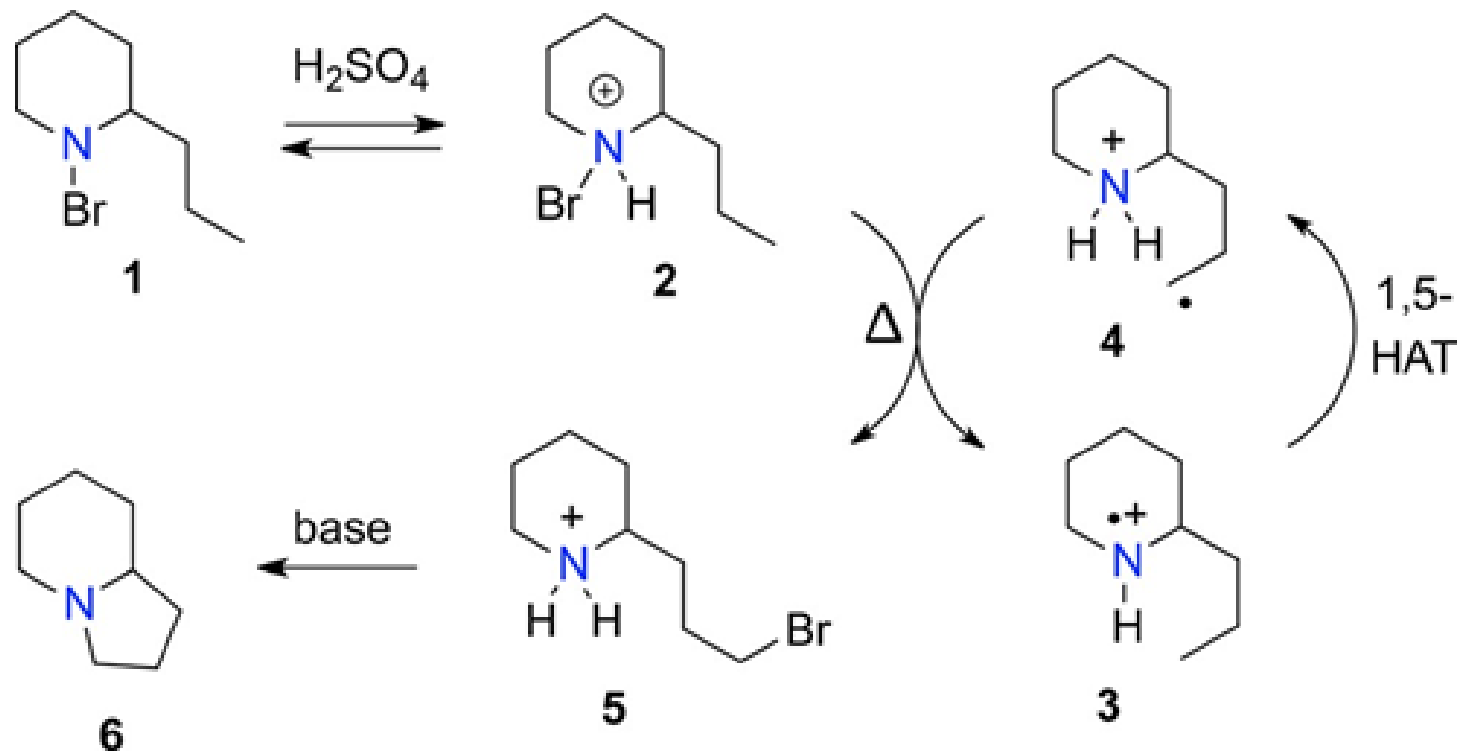
Voditelj: doc. dr. sc. Davor Šakić

Doktorand: Gabrijel Zubčić, mag. appl. chem.

Hofmann-Löffler-Freytagova reakcija

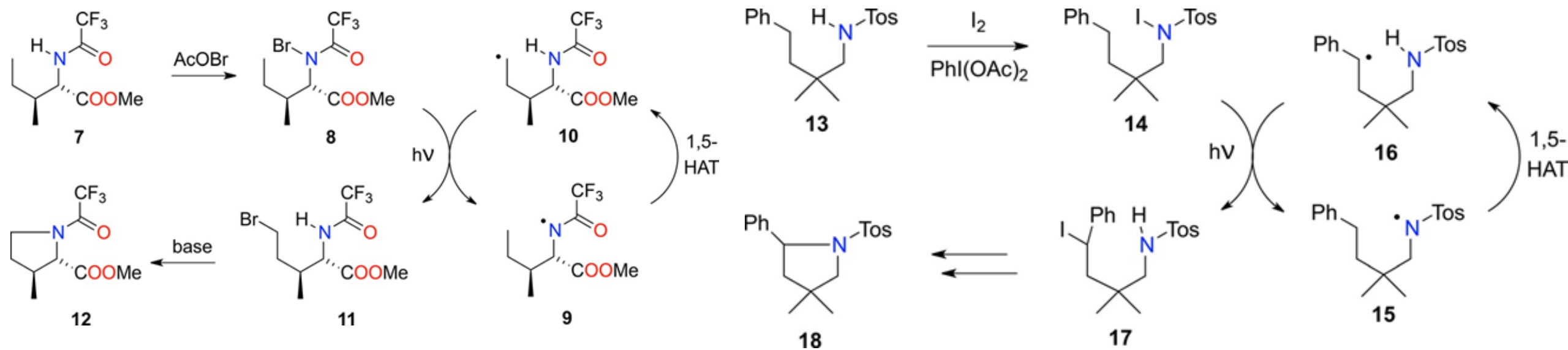
- Koristi se za C-H funkcionalizaciju.
- Produkt reakcije je pirolidin a rjeđe piperidin.
- Pripada tzv. “*Late stage functionalization*” metodama.
- Smjer razvoja-organokatalizirana reakcija u blagim uvjetima, u skladu s principima zelene kemije.

Izvorna Hofmann-Löffler-Freytagova reakcija



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

Modifikacije izvorne HLF reakcije



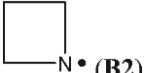
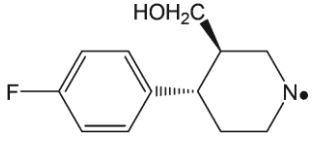
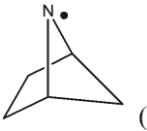
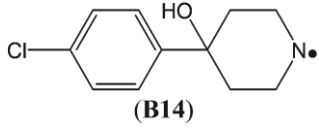
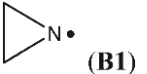
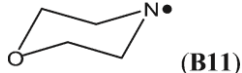
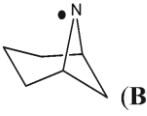
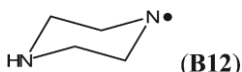
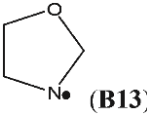
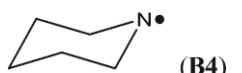
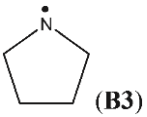
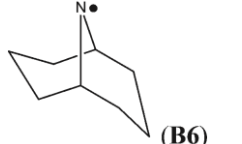
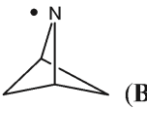
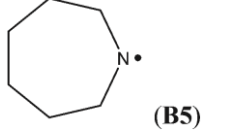
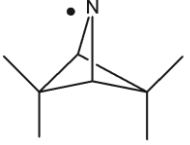
Reddy, L. R., Reddy, B. V. S., Corey, E. J. *Org. Lett.* **2006**, 8, 2819 – 2821.

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

Podloga projektu


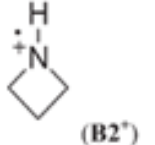
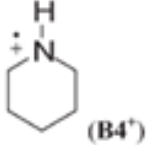
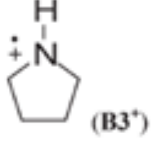
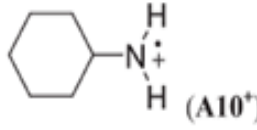
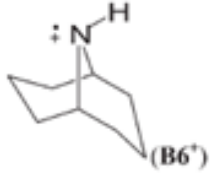
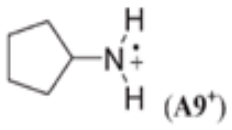
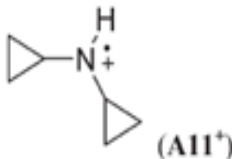
- Preliminarna istraživanja profesora Zipsea i docenta Šakića temeljena na kvantifikaciji koraka koji određuju brzinu HLF reakcije.
- Teorijski su izračunali radikalske stabilizacijske energije (eng. RSE) čitavog niza *N*-i *C*-radikala a samim time reakcijske entalpije i energije aktivacije ključnog HAT koraka.
- Demonstrirali su primjenu Bell-Evans-Polany-evog načela za familiju reakcija koje se odvijaju istim mehanizmom.

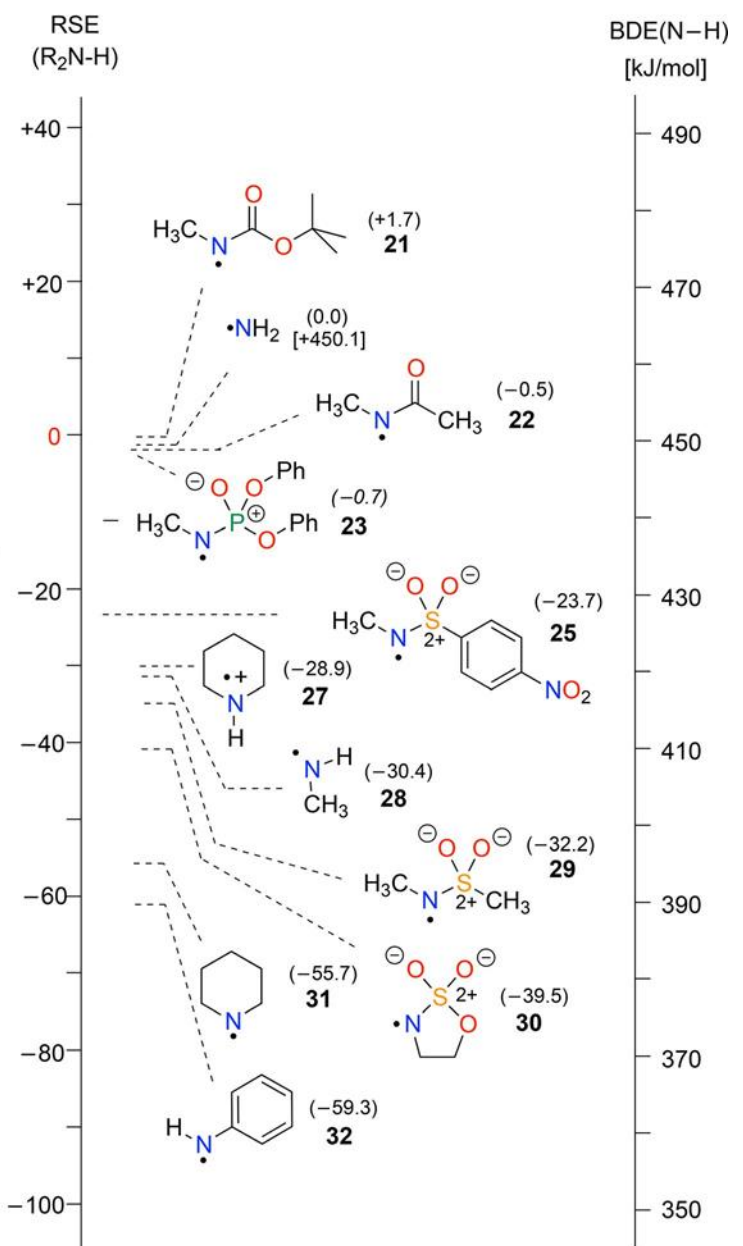
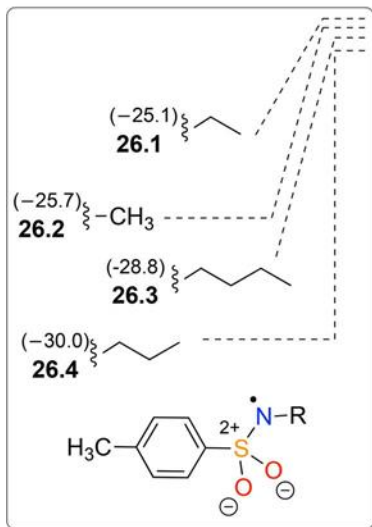
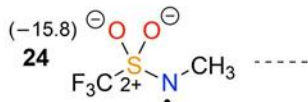
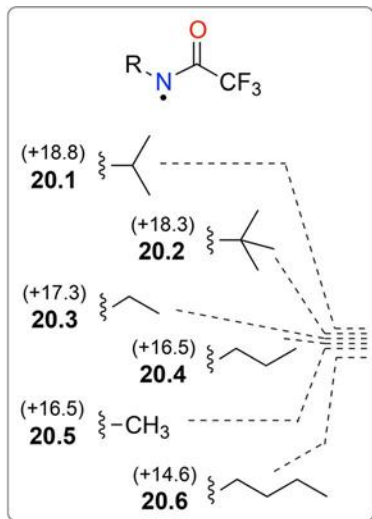
Radikalske stabilizacijske energije (eng .RSE) N- radikala

N-centered radical ^a	G3(MP2)-RAD	G3B3			
				-52.2	-52.6
	-42.0	-47.7		-53.2	-54.1
	-43.4	-44.2		-53.7	-54.3
	-47.8	-48.7		-54.6	-55.5
	-48.1	-49.3		-57.2	-57.8
	-49.7	-55.7		-63.7	-64.5
	-49.9	-51.1		-73.4	-74.7
	-51.9	-52.7		-85.3	-86.9

Hioe, J. Šakić, D. Vrčec, V. and Zipse, H., *Org. Biomol. Chem.*, **2015**, *13*, 157–169.

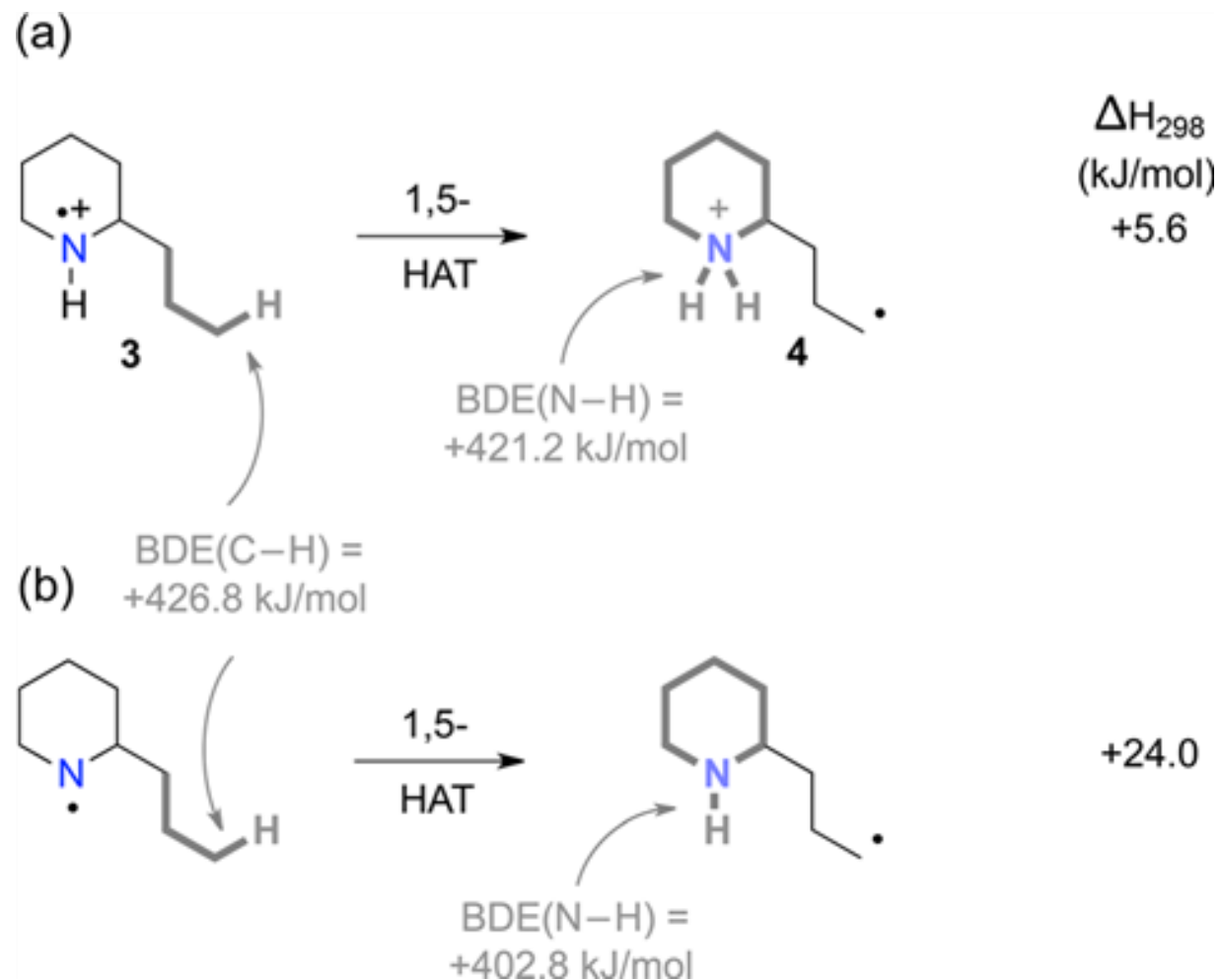
Radikalske stabilizacijske energije (eng .RSE) N- radikal kationa

N-centered radical cation ^a	G3(MP2)-RAD	G3B3	N-centered radical cation ^a	G3(MP2)-RAD	G3B3	Other ^b
 (B1 ⁺)	+48.8	+48.6	[*] NH ₂ (A0)	0.0	0.0	0.0
 (B2 ⁺)	-15.5	-15.7	⁺ NH ₃ (A0 ⁺)	+72.0	+73.2	+73.0 (0 K, W2w)
 (B4 ⁺)	-28.0	-28.9	⁺ NH ₂ CH ₃ (A1 ⁺)	+11.1	+13.7	+10.7 (0 K, W2w)
 (B3 ⁺)	-35.3	-35.8	 (A10 ⁺)	-0.6	-1.6	—
 (B6 ⁺)	-35.6	-37.0	 (A9 ⁺)	-9.2	-10.1	—
			⁺ NH(CH ₃) ₂ (A3 ⁺)	-23.6	-23.7	-27.9 (0 K, W2w)
			 (A11 ⁺)	-95.4	-96.4	—

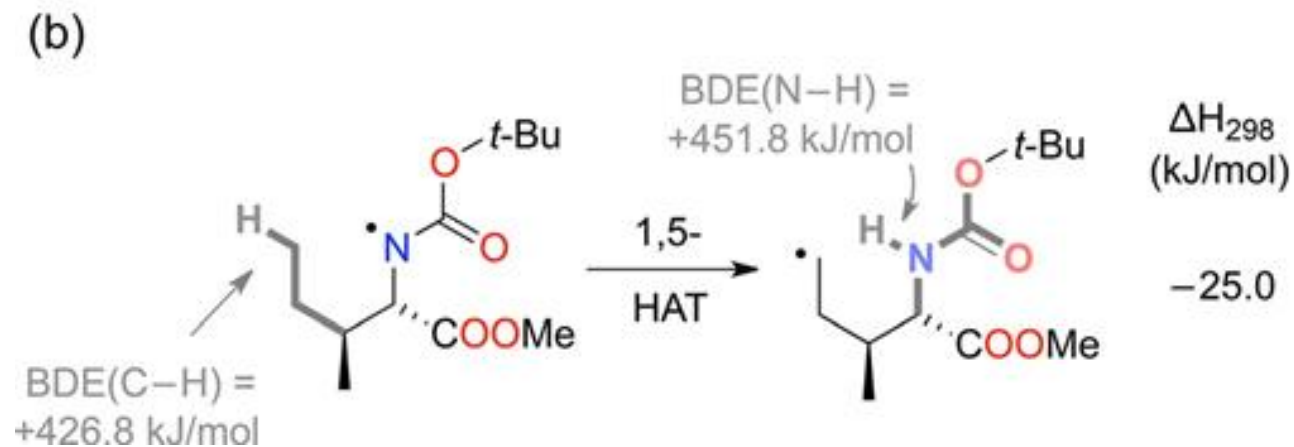
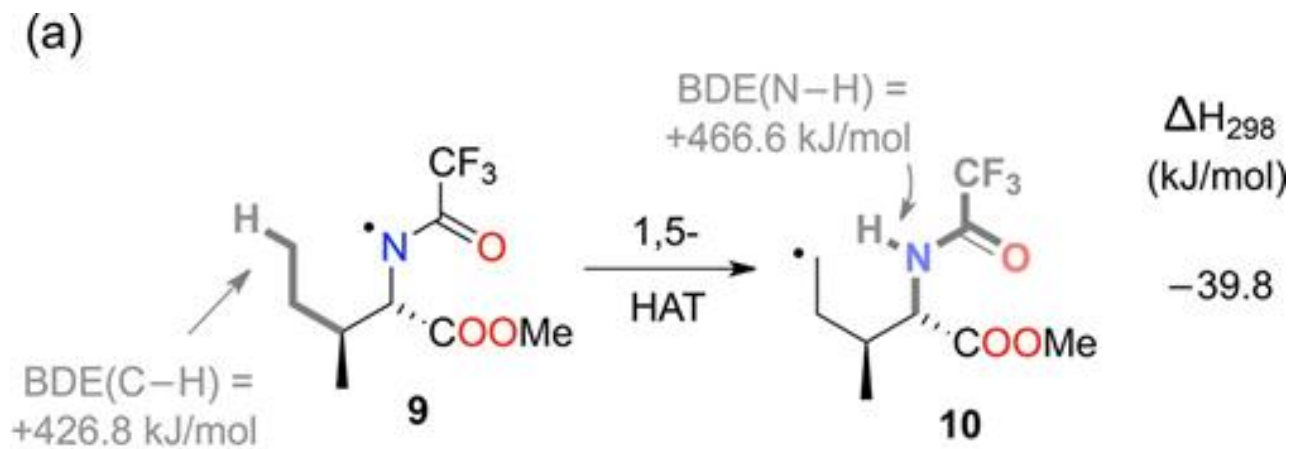


Radikalske stabilizacijske energije (RSE) i energije disocijacije veza (BDE) za N-radikale

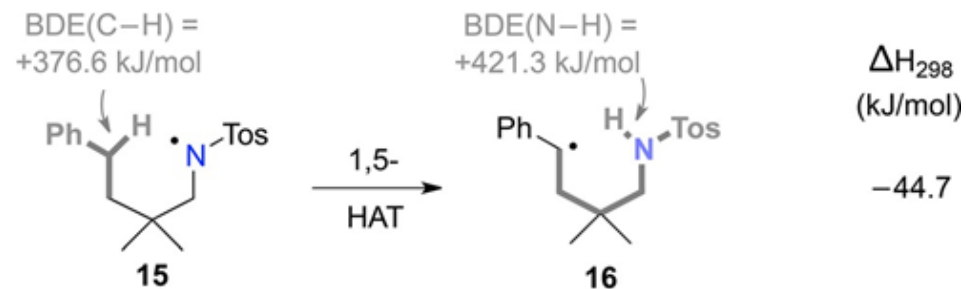
Utjecaj kiseline na termokemijski profil 1,5 HAT koraka; klasična HLF reakcija



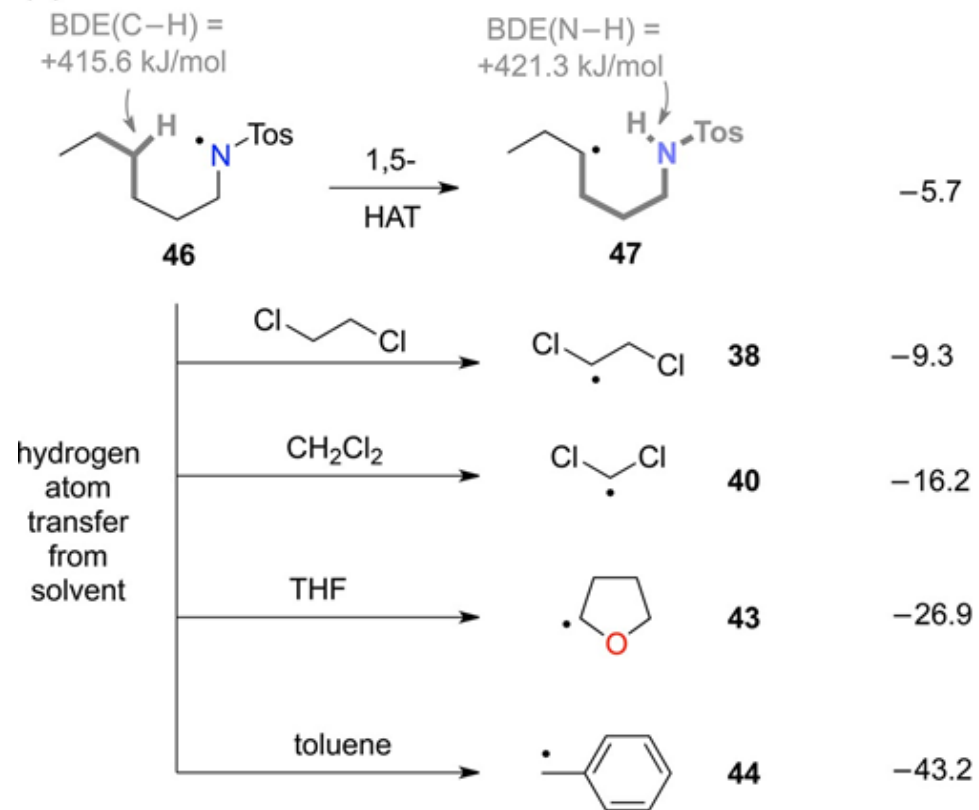
Termokemijski profil 1,5 HAT koraka; Corey-eva modifikacija



(a)



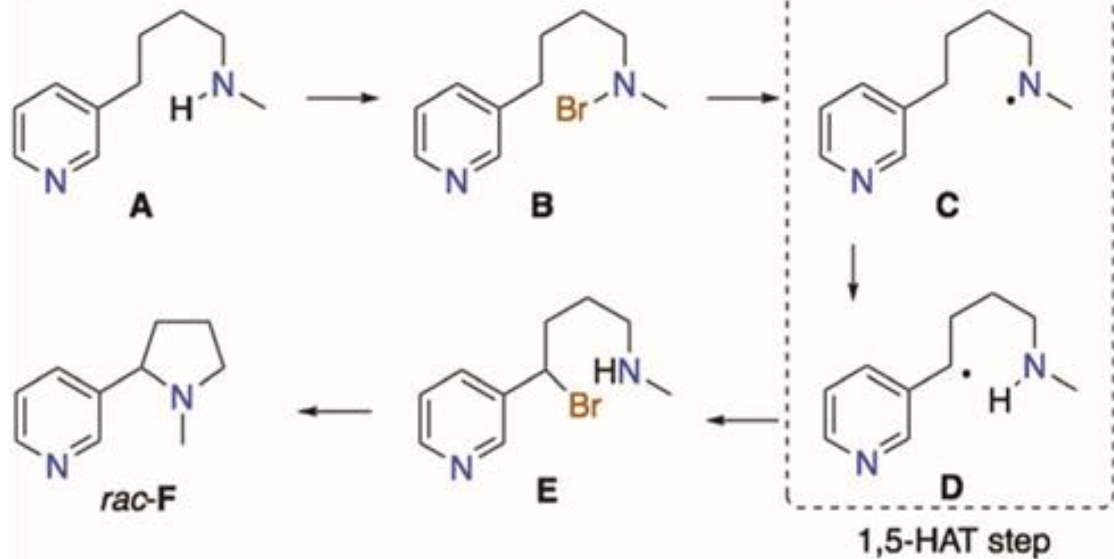
(b)



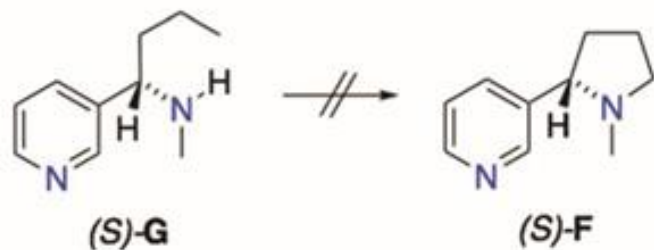
Termokemijski profil 1,5 HAT koraka; Suarez-ova modifikacija; interakcija s molekulama otapala.

Analiza protokola za sintezu nikotina

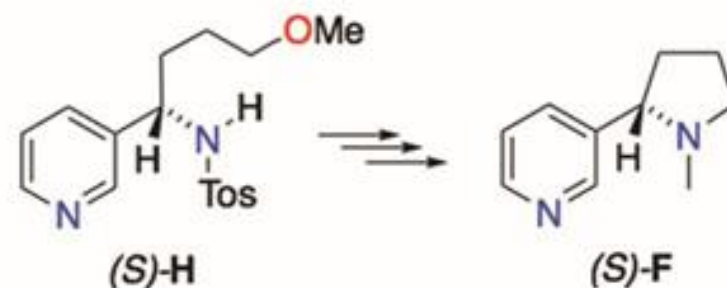
(a) Löffler and Kober, 1909



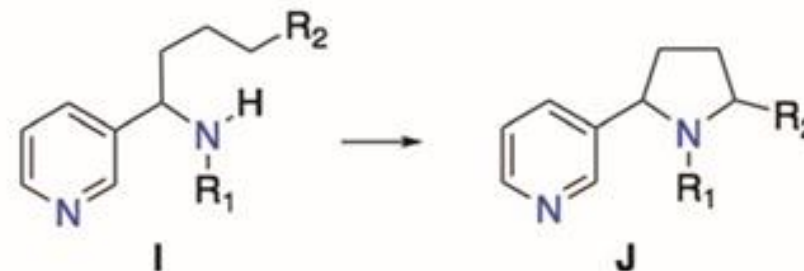
(b) Löffler and Kober, 1909



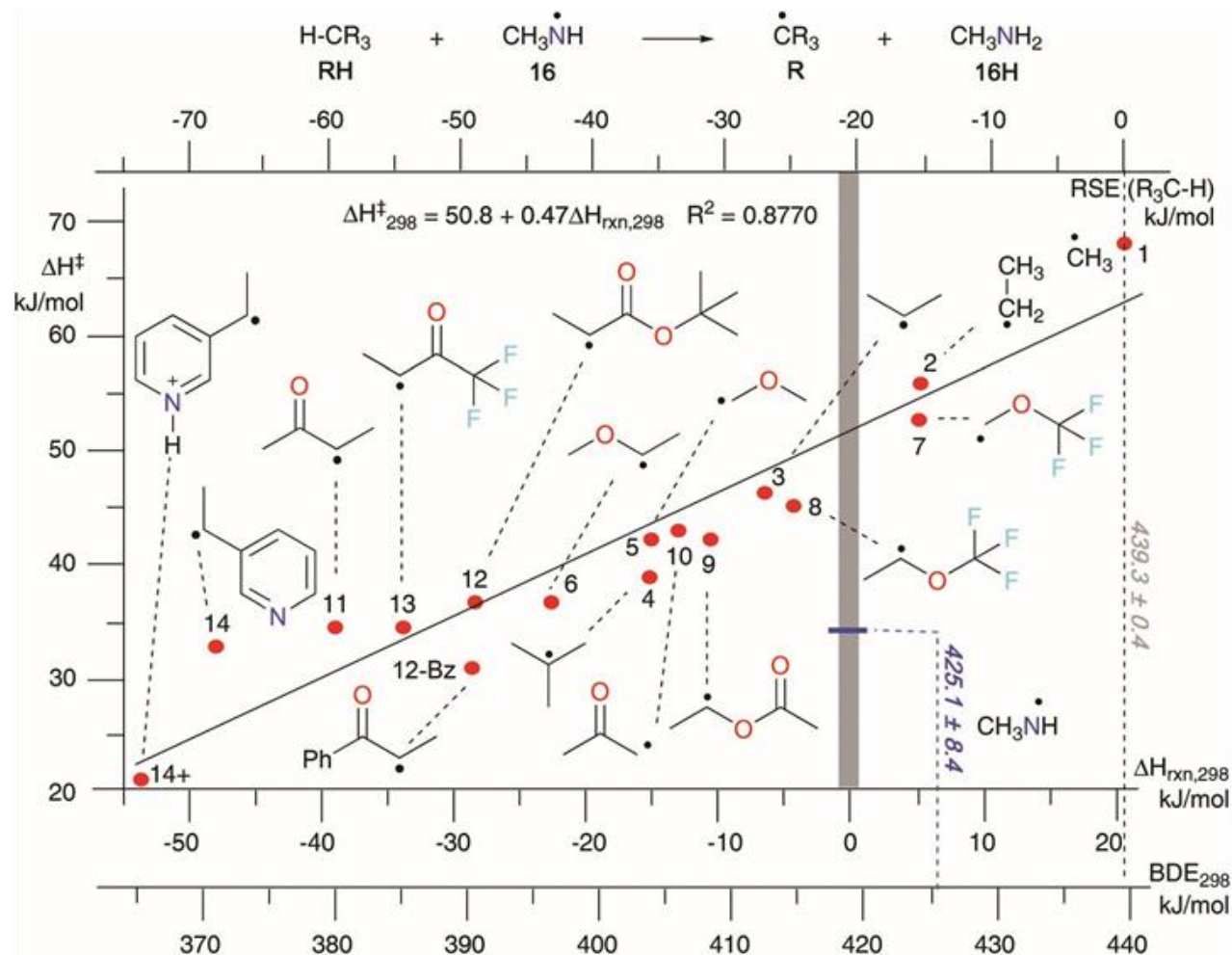
(c) Del Castillo and Muniz, 2019



(d) This work

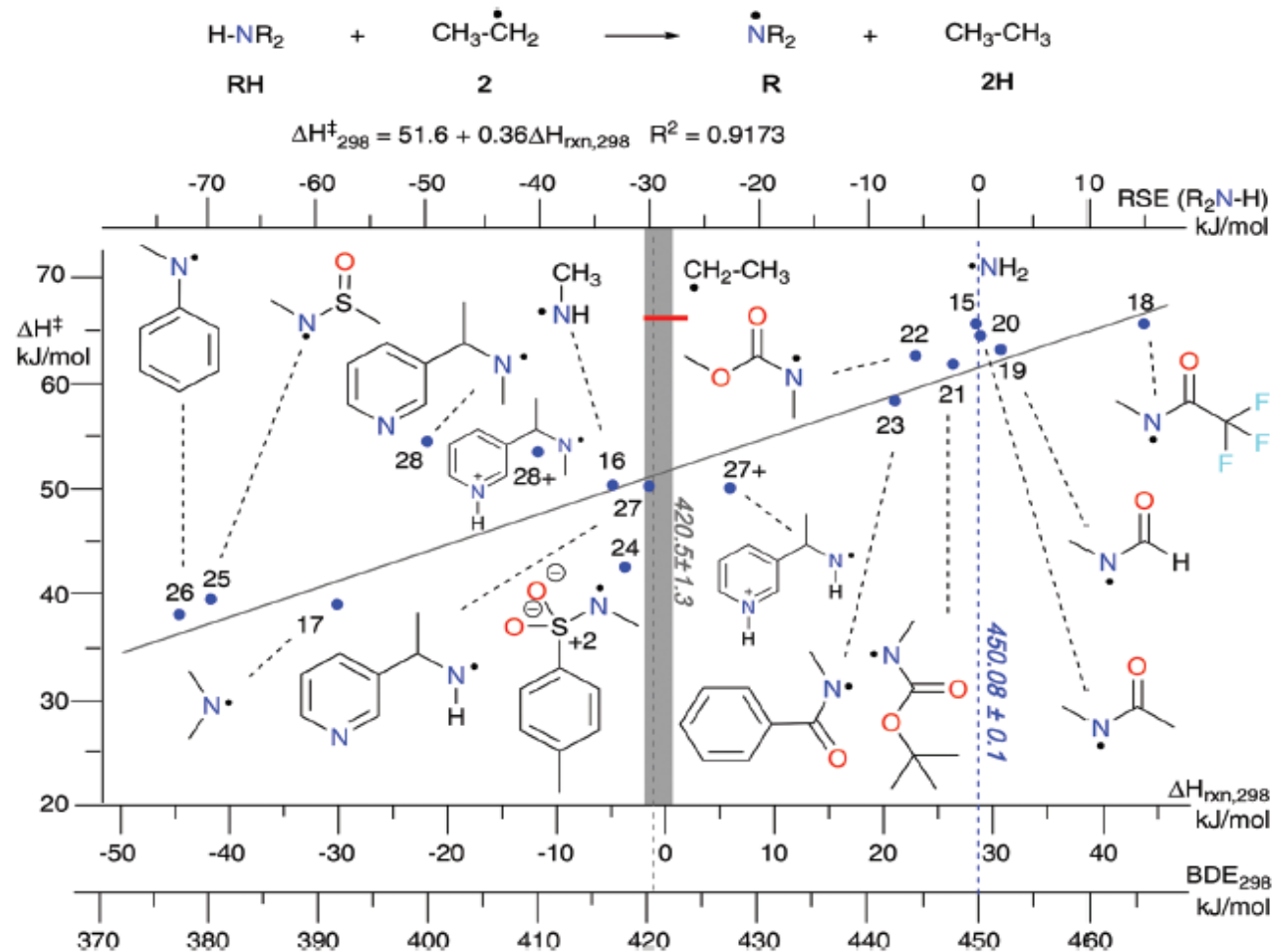


Stabilnost C-radikala (Izračuni za fragmente); Demonstracija Bell-Evans-Polanyi-jevog principa

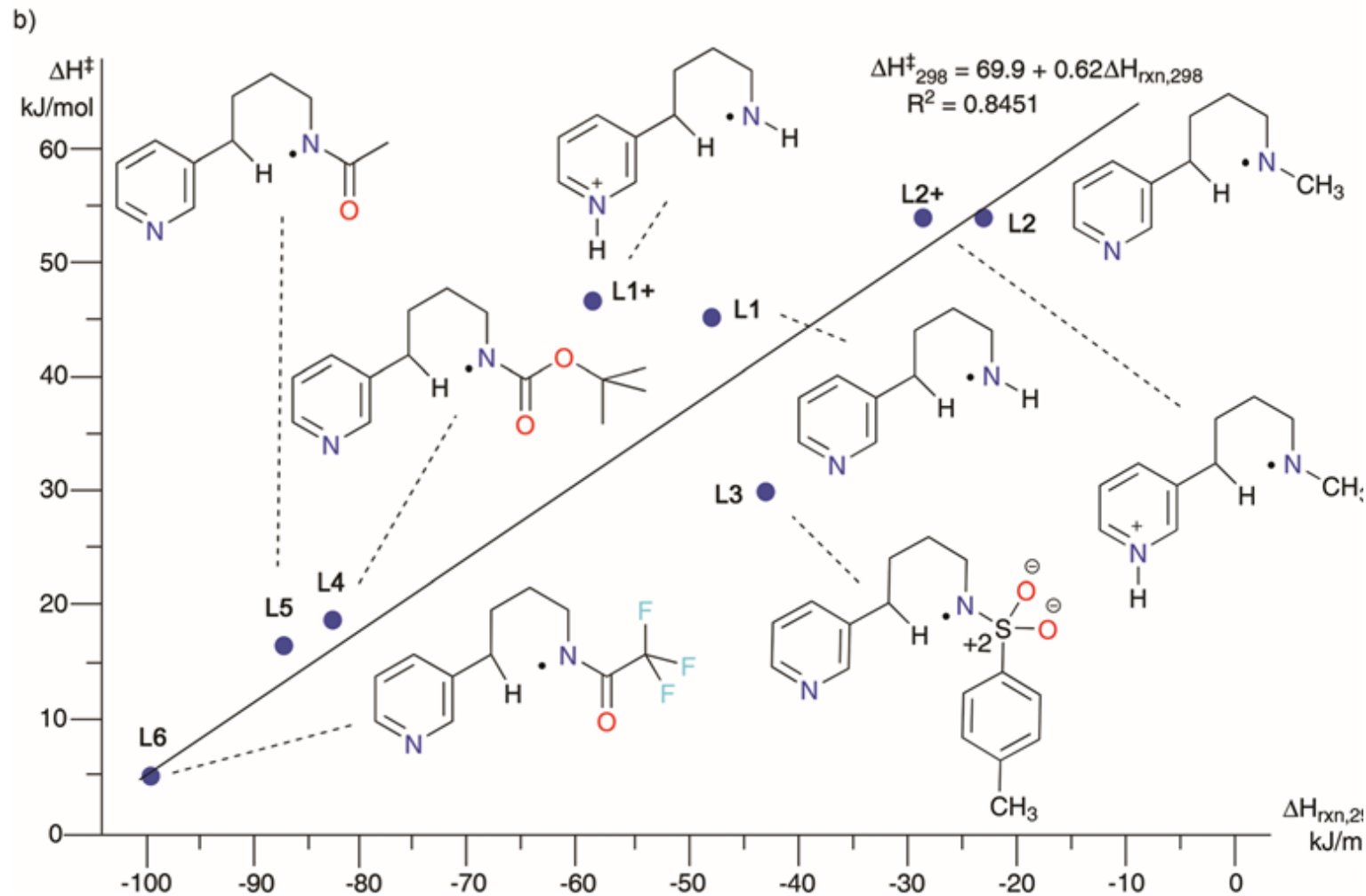


S. Shkunnikova, H. Zipse, D. Šakić, *Org. Biomol. Chem.* **2021**, *19*, 854–865.

Stabilnost N-radikala (Izračuni za fragmente); Demonstracija Bell-Evans-Polanyi-jevog principa

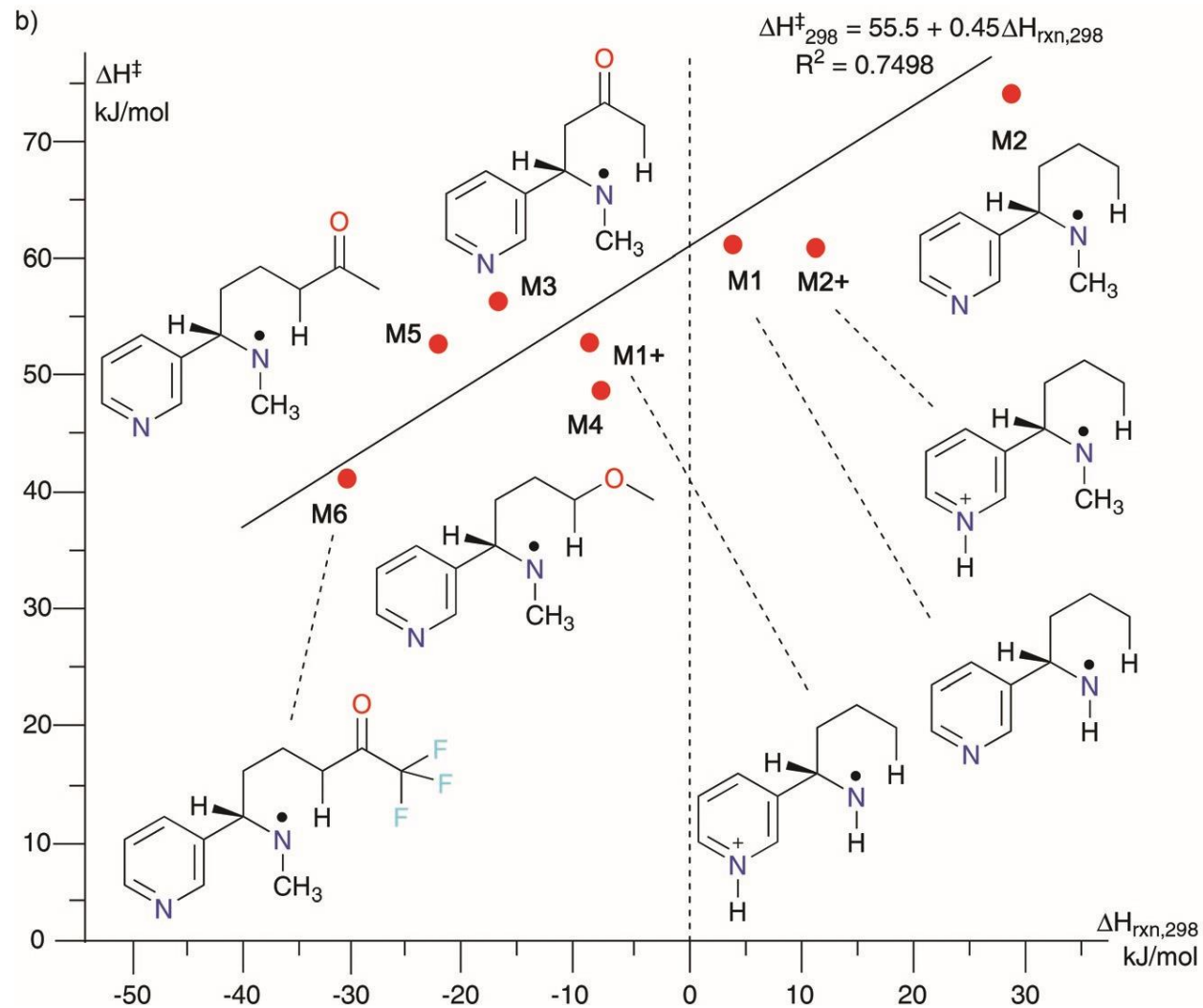


Stabilnost N-radikala (Izračuni za cijele supstrate); Protokol Löfflera i Kobera

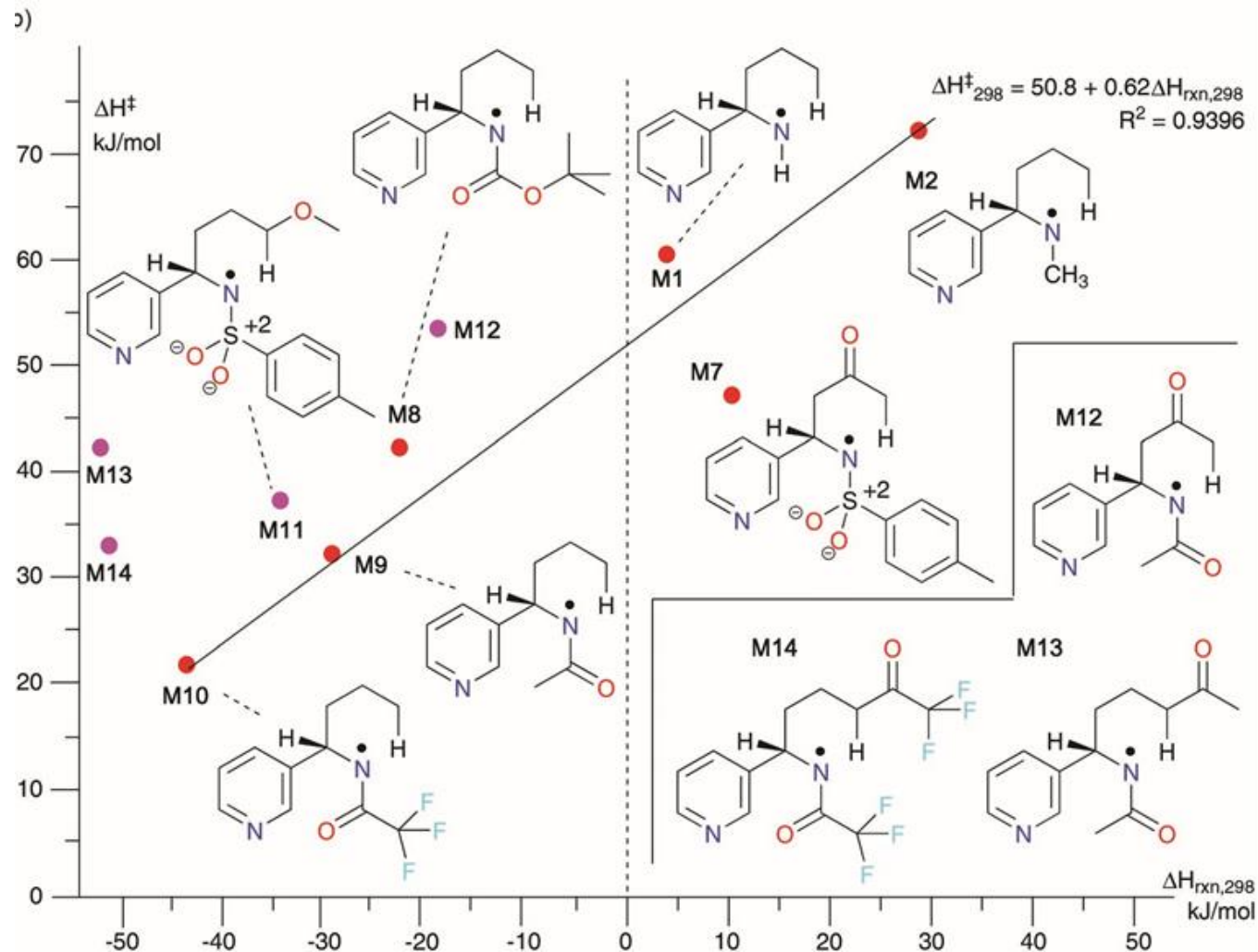


S. Shkunnikova, H. Zipse, D. Šakić, *Org. Biomol. Chem.* **2021**, *19*, 854–865.

Stabilnost C-radikala(izračuni za cijele supstrate); Protokol Del Castilla i Muñiza



Stabilnost N-radikala (izračuni za cijele supstrate); Protokol Del Castilla i Muñiza



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

Ciljevi projekta

Razvijanje znanja o parametrima koji vode modernu HLF reakciju:

- Ispitivanje jakosti halogenih oksidansa u koraku *N*-aktivacije
- Promjena vremena reakcije
- Izloženost zračenju odabranih valnih duljina
- Temperaturni efekti, efekti otapala
- Pročišćavanje produkata reakcije

Ciljevi projekta

Definiranje nekoliko prekidača:

- 1,5- ili 1,6-HAT regioselektivnost.
- Radikalni ili ionski mehanizam
- Inter- ili intramolekularni mehanizam

Ciljevi projekta

- Uobičajena praksa organske sinteze temelji se na metodi pokušaja i pogreške → dugotrajno.
- Sinergijskim djelovanjem kvatno-kemijskih metoda i kinetičkih eksperimenata → predvidjeti reakcijski put te smanjiti vrijeme potrebno za dobivanje ispravnog protokola za sintezu.

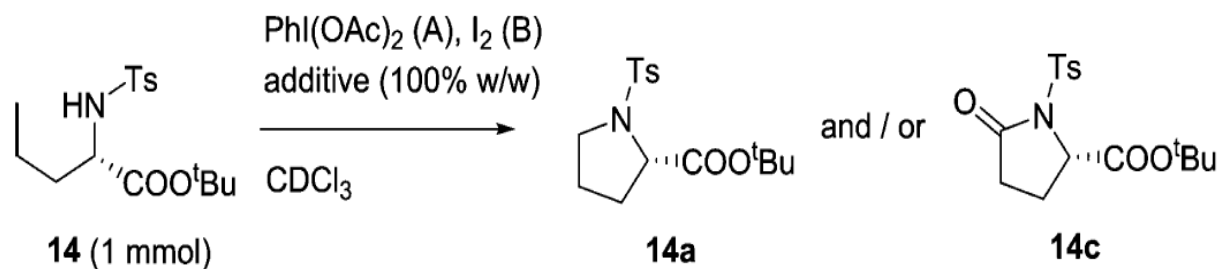
Konkurencija- učinci otapala

Chemoselective Intramolecular Functionalization of Methyl Groups in Nonconstrained Molecules Promoted by *N*-Iodosulfonamides

Nieves R. Paz,[†] Dionisio Rodríguez-Sosa,[†] Haydee Valdés,[§] Ricardo Marticorena,[†] Daniel Melián,[‡] M. Belén Copano,[†] Concepción C. González,^{*,†} and Antonio J. Herrera^{*,†}

Letter

Table 2. NMR-Monitored Experiments with 14



Konkurencija- 1,5-HAT ili 1,6-HAT regioselektivnost

OL Organic Letters


Cite This: *Org. Lett.* XXXX, XXX, XXX–XXX

ACS Editors' Choice

Letter


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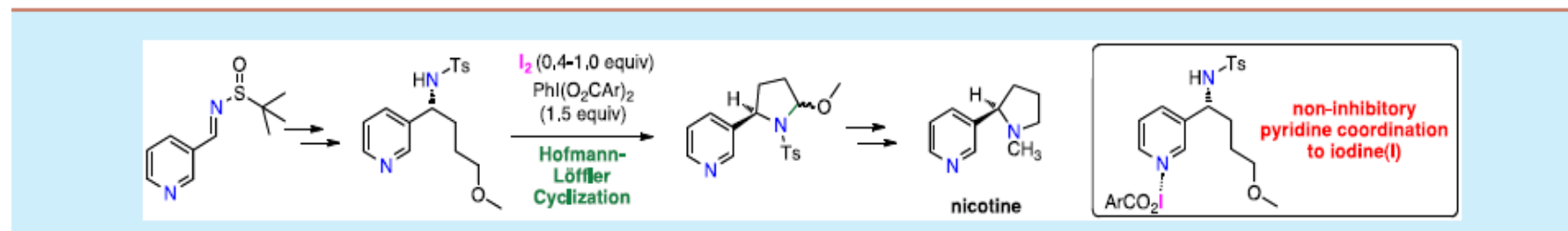
Enantioselective Synthesis of Nicotine via an Iodine-Mediated Hofmann–Löffler Reaction

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

[†]Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Av. Països Catalans 16, 43007 Tarragona, Spain

[‡]ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain

 Supporting Information



Konkurencija- 1,5-HAT ili 1,6-HAT regioselektivnost


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^{*,†,§}

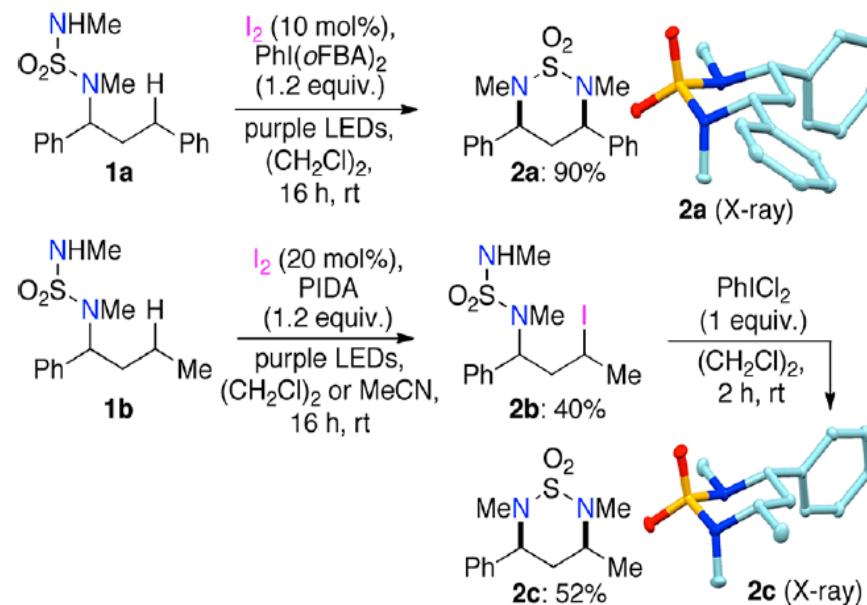
[†]Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, 16 Avgda. Països Catalans, 43007 Tarragona, Spain

[‡]Universidad de Oviedo, Julian Clavería, s/n, 33006 Oviedo, Spain

[§]ICREA, Pg. Lluís Companys 23, 08010 Barcelona, Spain

 Supporting Information

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



Konkurencija- 1,5-HAT ili 1,6-HAT regioselektivnost



Journal Name

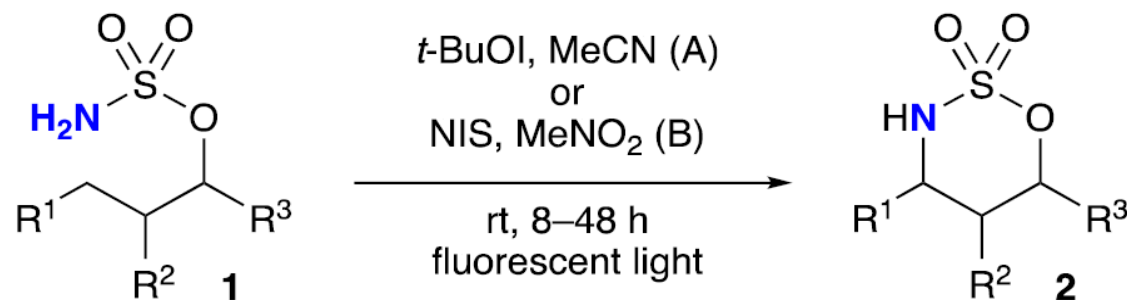
COMMUNICATION

Transition-Metal-Free Intramolecular C–H Amination of Sulfamate Esters and *N*-Alkylsulfamides

Received 00th January 20xx,
Accepted 00th January 20xx

Kensuke Kiyokawa,* Shogo Nakamura, Keisuke Jou, Kohji Iwaida, and Satoshi Minakata *

DOI: 10.1039/x0xx00000x



Konkurencija- 1,6-HAT ili 1,7-HAT regioselektivnost

Chemical
Science



EDGE ARTICLE





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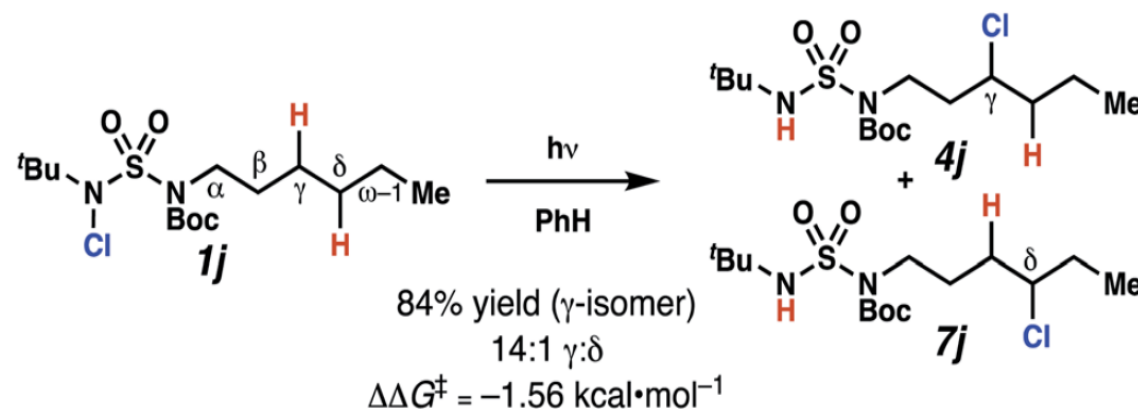
Sulfamides direct radical-mediated chlorination of aliphatic C–H bonds†

Cite this: *Chem. Sci.*, 2020, 11, 217

All publication charges for this article have been paid for by the Royal Society of Chemistry

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

C. Reaction outcome suggests that 1,6- and 1,7-HAT processes are competitive



Scheme 3 1,6- and 1,7-HAT processes appear competitive.

Polihalogeniranje; 1,5-HAT

Chemistry - A European Journal

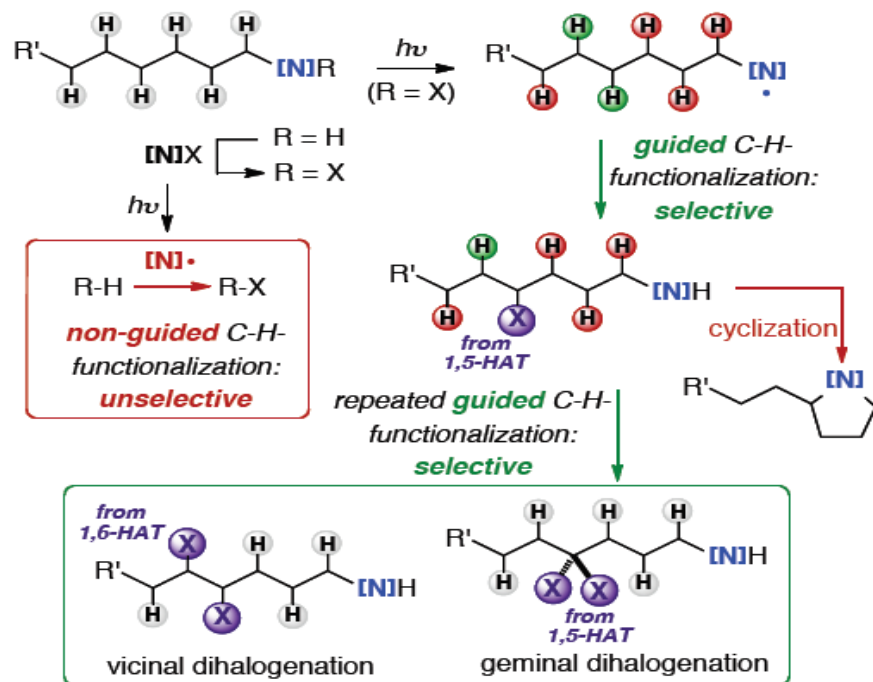
10.1002/chem.201804504

COMMUNICATION

WILEY-VCH

Multiple Halogenation of Aliphatic C-H Bonds within the Hofmann-Löffler Manifold

Estefanía Del Castillo,^[a,+] Mario D. Martínez,^[a,+] Alexandra E. Bosnidou,^[a] Thomas Duhamel,^[a,b] Calvin Q. O'Broin,^[a] Hongwei Zhang,^[a] Eduardo C. Escudero-Adán,^[a] Marta Martínez-Belmonte,^[a] Kilian Muñiz^{*[a,c]}



Konkurencija- inter- ili intramolekularni mehanizam

ACS Catalysis

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Letter

Selective Piperidine Synthesis Exploiting Iodine-Catalyzed Csp³-H Amination under Visible Light

Hongwei Zhang, and Kilian Muniz

ACS Catal., Just Accepted Manuscript • Publication Date (Web): 10 May 2017

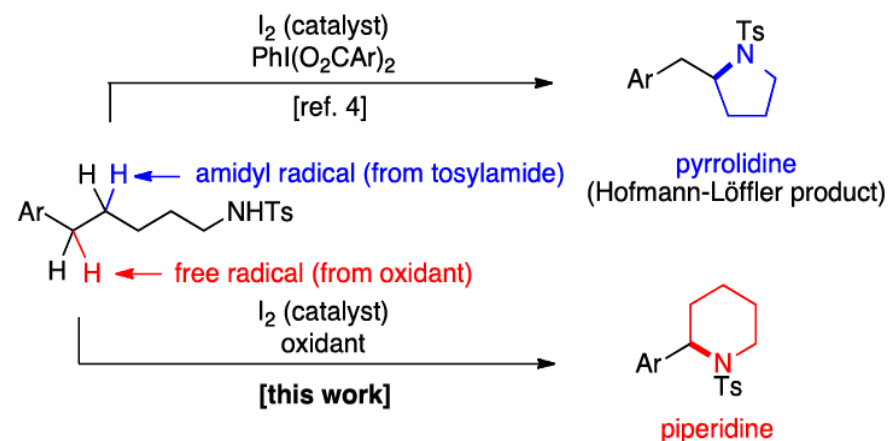


Figure 1. Position-selective intramolecular C-H amination for pyrrolidine and piperidine synthesis.

Konkurencija- inter- ili intramolekularni mehanizam

OL Organic Letters

Cite This: *Org. Lett.* XXXX, XXX, XXX-XXX

Letter

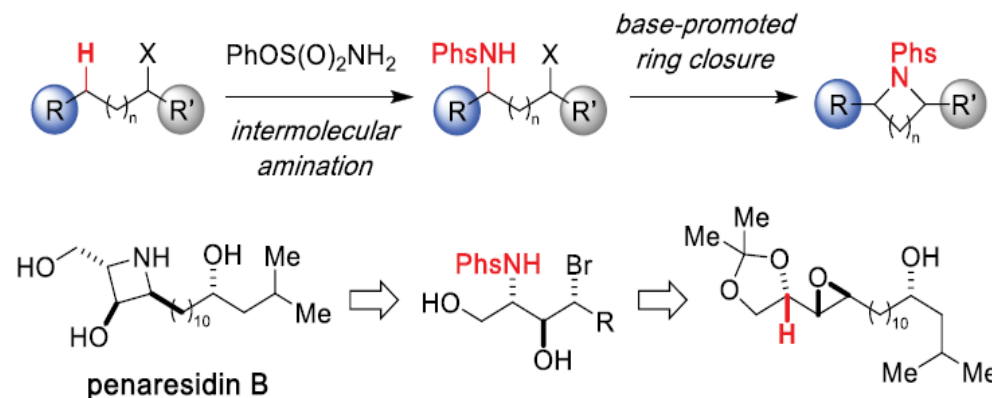
pubs.acs.org/OrgLett

Intermolecular sp^3 -C–H Amination for the Synthesis of Saturated Azacycles

Kerry N. Betz,[†] Nicholas D. Chiappini,^{†,‡} and J. Du Bois^{*,†}

Department of Chemistry, Stanford University, 337 Campus Drive, Stanford, California 94305, United States

Scheme 1. Selective Intermolecular C–H Amination for the Preparation of Cyclic Amines, Including Polyfunctionalized Azetidines



Kontroversa-Radikaliski ili ionski mehanizam

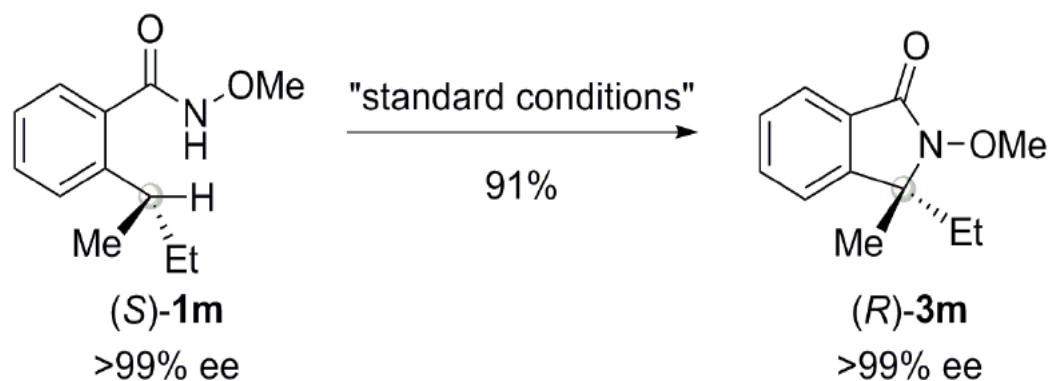
J|A|C|S
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Communication

Iodoarene-Catalyzed Stereospecific Intramolecular sp^3 C-H Amination: Reaction Development and Mechanistic Insights

Chendan Zhu, Yong Liang, Xin Hong, Heqing Sun, Wei-Yin Sun, K. N. Houk, and Zhuangzhi Shi



Hvala na pažnji!