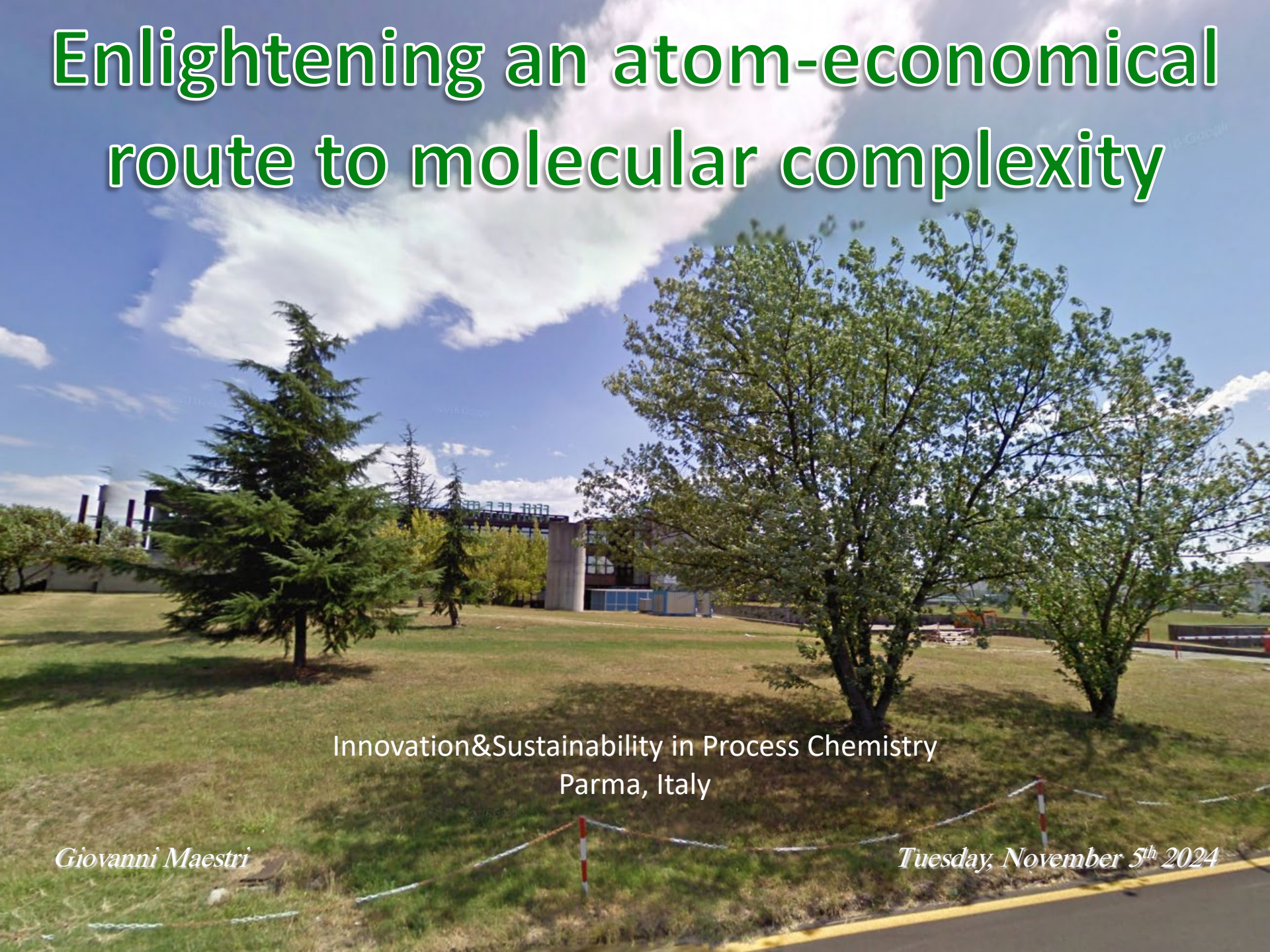
Enlightening an atom-economical route to molecular complexity



Innovation&Sustainability in Process Chemistry
Parma, Italy

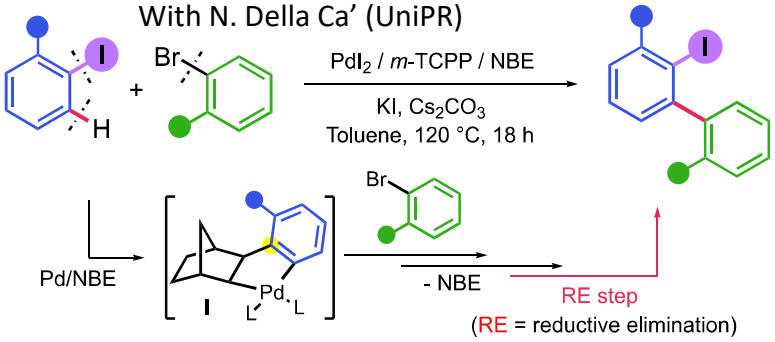
Giovanni Maestri

Tuesday, November 5th 2024

4 X 4 OVERVIEW

ACIE **2023** *62* e202218928

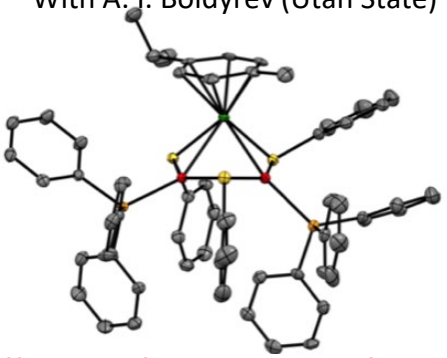
With N. Della Ca' (UniPR)



Pd-norbornene joint catalysis

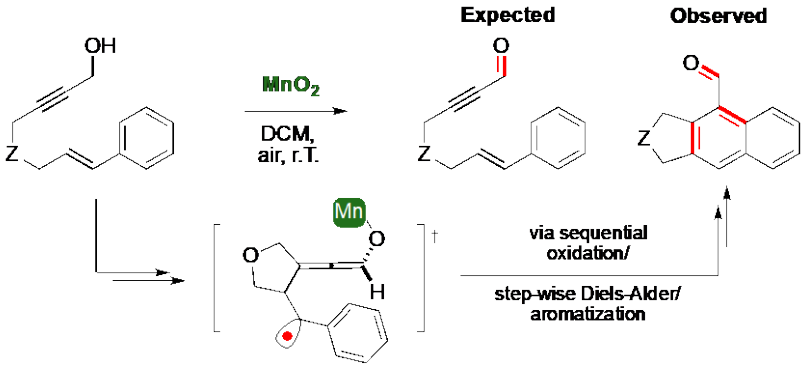
Chem Sci **2021** *12* 477

With A. J. Boldyrev (Utah State)



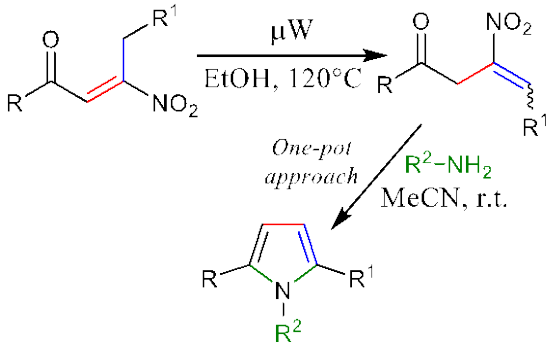
All-metal aromatic clusters

Catalytic synthesis



Org Lett **2021** *23* 6536

Mechanistic studies

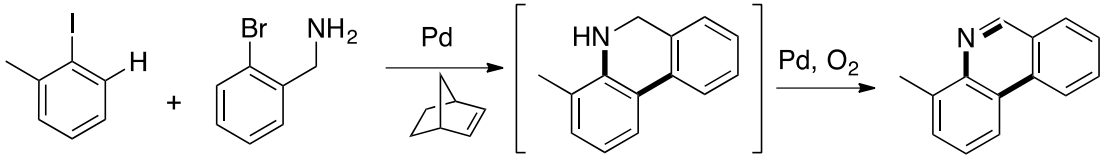


With A. Palmieri (UniCAM)

Adv Synth Catal **2020** *362* 4680

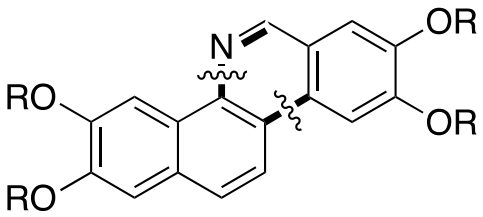
PROS AND CONS OF CROSS-COUPLING: AN EXAMPLE FROM THE CATELLANI REACTION

A model reaction with Pd/norbornene joint catalysis



Org Lett **2010** *12* 5692

A few interesting targets with relevant biological activities



Natural benzo[c]phenanthridines:
Norallonitidine, Noravicine, Nornitidine…

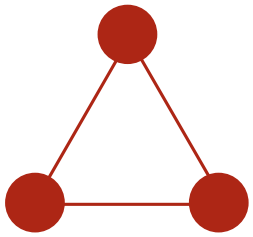
Some drawbacks

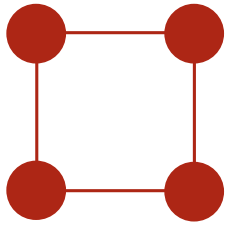
1 mol prod (+$),
1 mol HI (-$), HBr (-$)
2 mol base (-$)

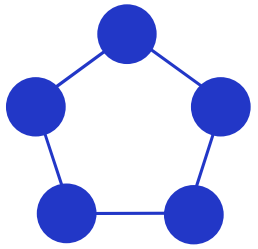
Low atom-economy (Trost),
Low E-factor (Sheldon)

OUTLINE: ATOM-ECONOMICAL CYCLIZATION STRATEGIES

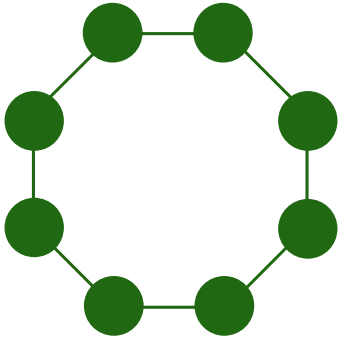
Small rings

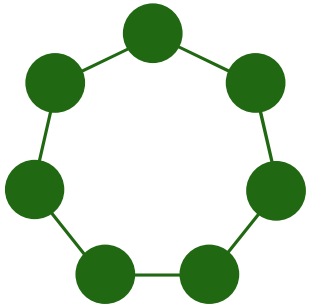


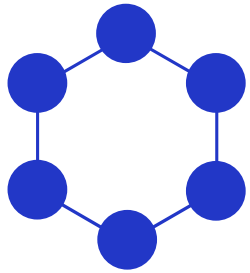




Common rings



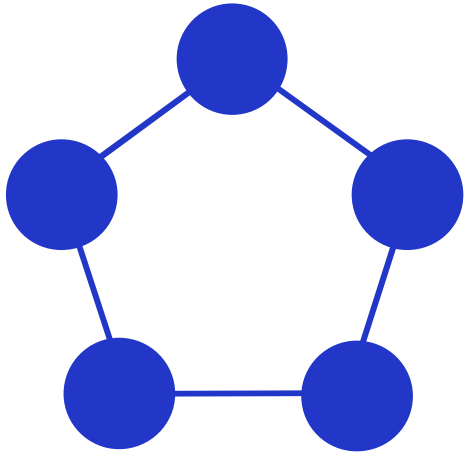




Medium rings

An old lesson from the food valley around Parma: do not produce wastes!

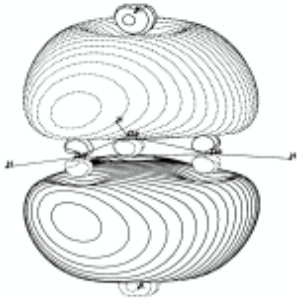
FIVE-MEMBERED RINGS



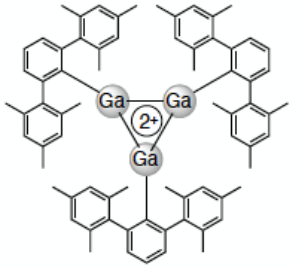
CATALYSIS WITH ALL-METAL AROMATICS

TRINUCLEAR ALL-METAL AROMATICS

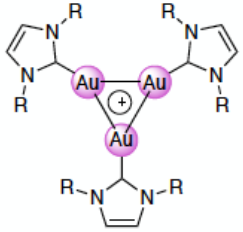
1865 - Kekulé - Introduces the concept of aromaticity
1979 - Bursten and Fenske - Introduce the concept of metalloaromaticity
1982 - Elliot - First stable metallobenzene, osmabenzene
1995 - Robison - First aromatic cluster $[Ga_3]^{2-}$



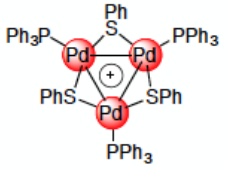
MO of $K_2[GaH]_3$



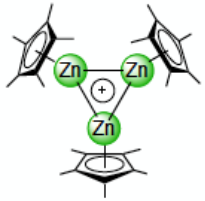
Robison 1995
AOp π-orbital



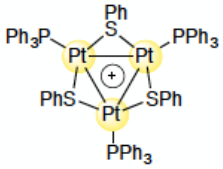
Sadighi 2012
AOs σ-orbital



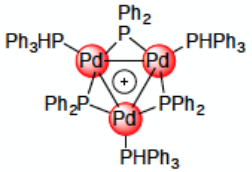
Maestri 2014
AOd δ-orbital



Fischer 2015
AOs σ-orbital



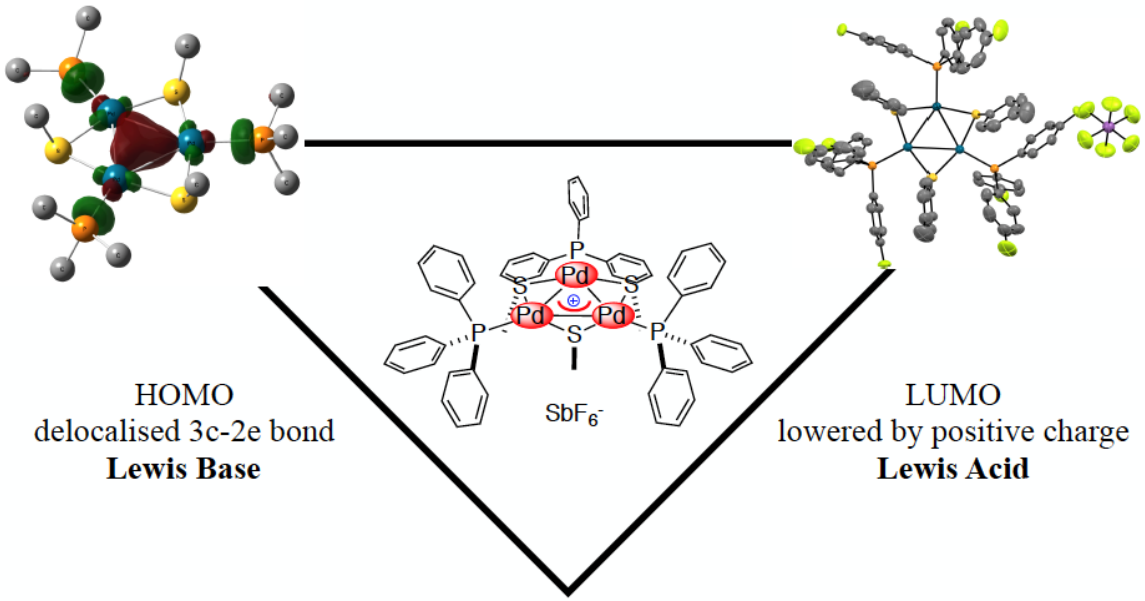
Maestri 2015
AOd δ-orbital

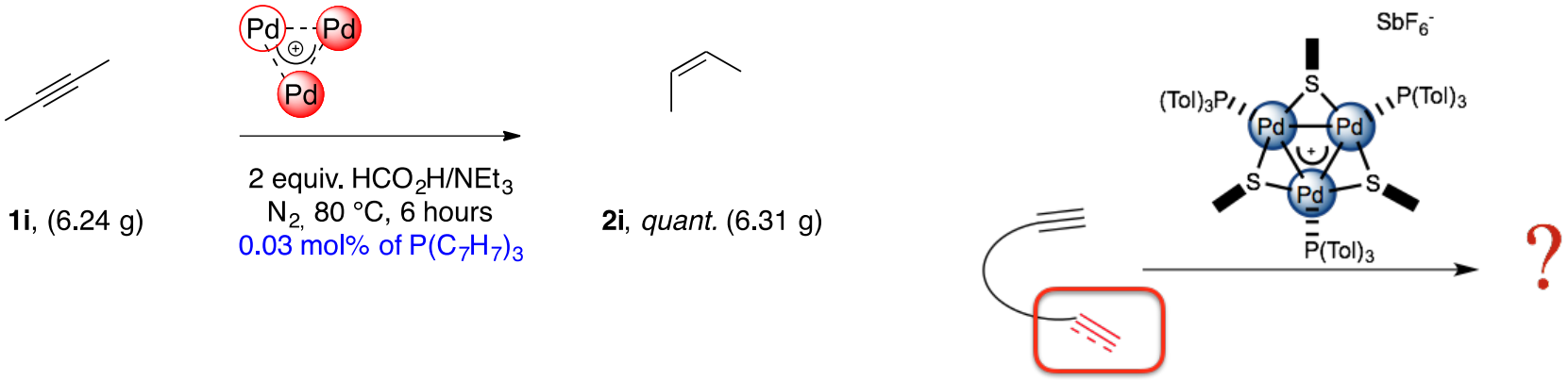


Schoenebeck 2019
AOd δ-orbital

Robinson *JACS* **1995**, 117, 7578; Sadighi *ACIE* **2012**, 51, 12077; Maestri *ACIE* **2014**, 53, 1987; Fischer *ACIE* **2015**, 54, 4370; Maestri *Chem. Eur. J.* **2015**, 21, 12271; Schoenebeck *ACIE* **2019**, 58, 211

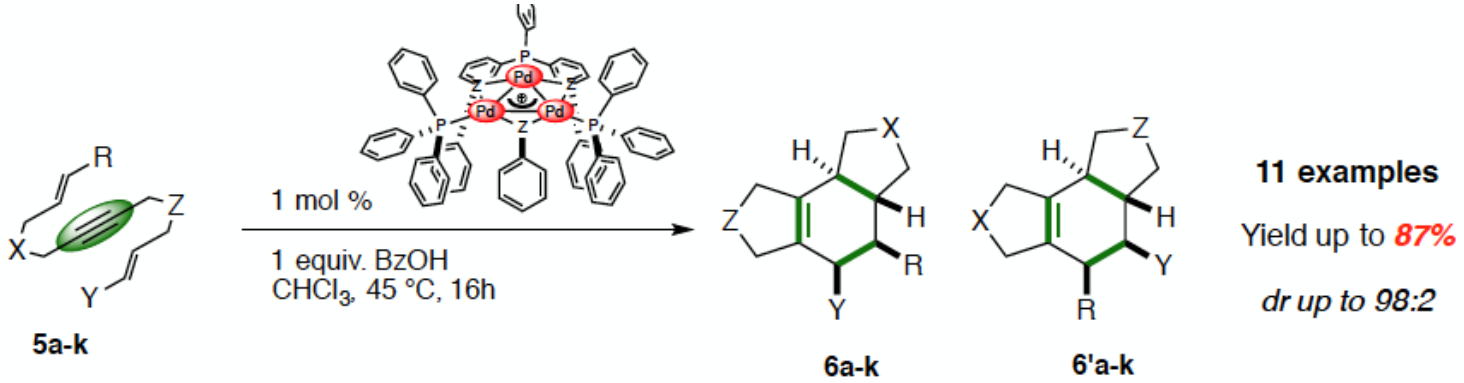
CATALYSIS WITH M_3^+: FROM SEMI-REDUCTIONS TO FORMATION OF C-C BONDS

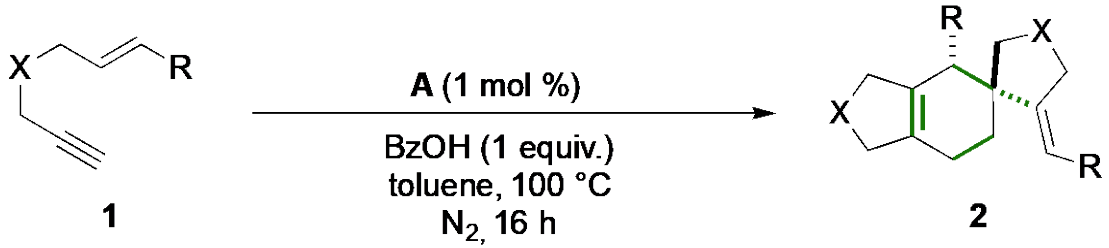


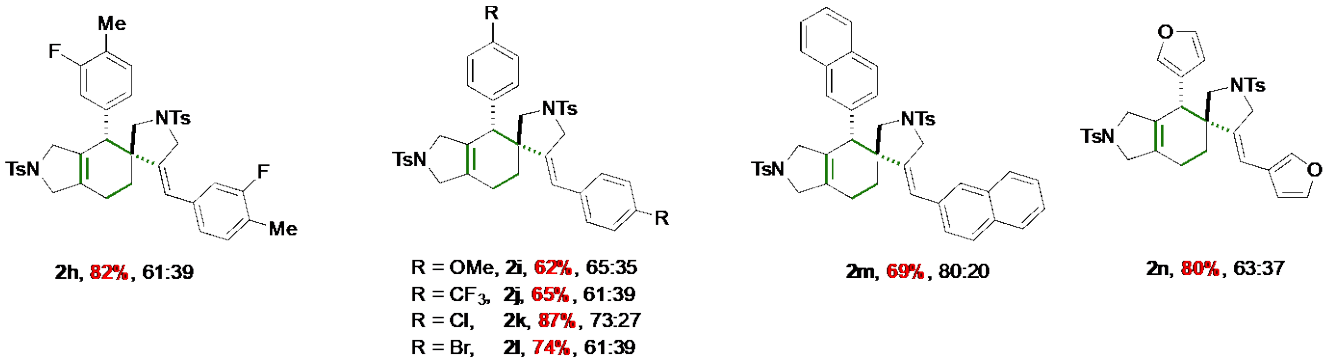


ChemCatChem **2015** *7* 3266 *Dalton Trans.* **2016** *45* 15786 *ACS Sustainable Chem. & Eng.* **2017** *5* 8205

REACTIVITY WITH DIENYNES AND DIMERIZATION WITH 1,6-ENYNES

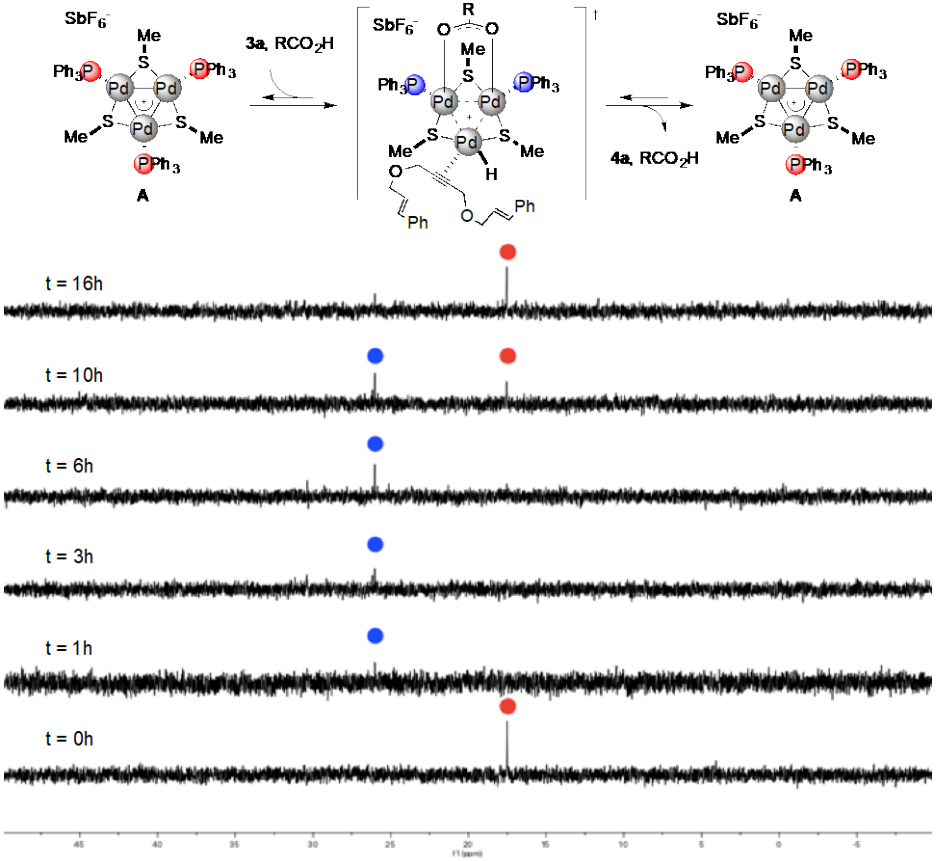


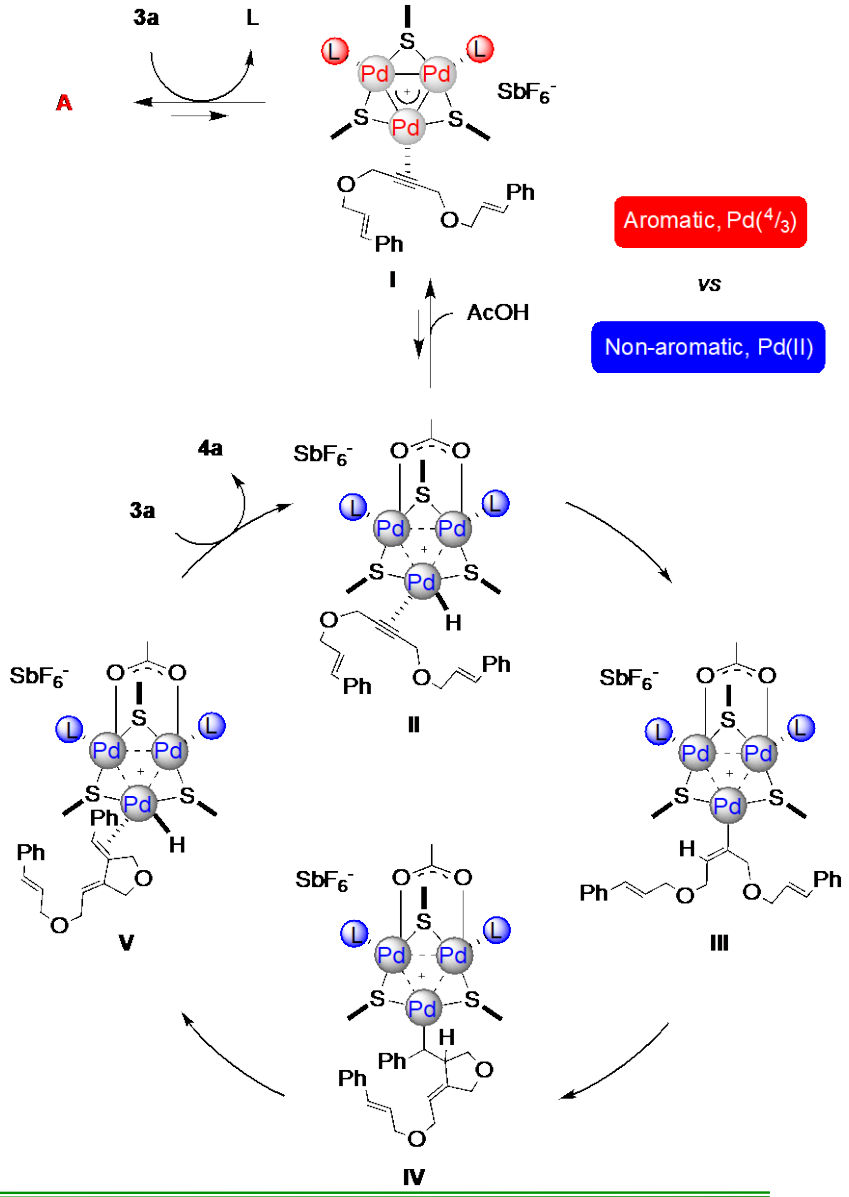




ACS Catalysis, **2018**, *8, 144* *JOC* **2021** *86* 15433

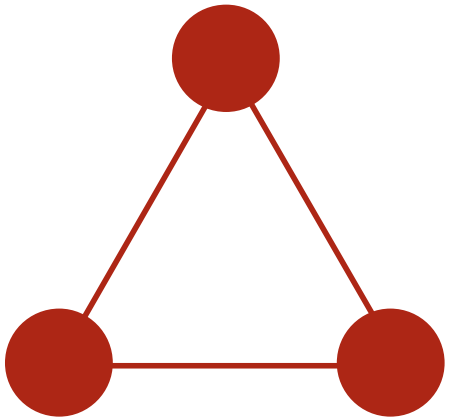
MECHANISTIC STUDIES: AROMATICITY ENSURES CATALYST STABILITY





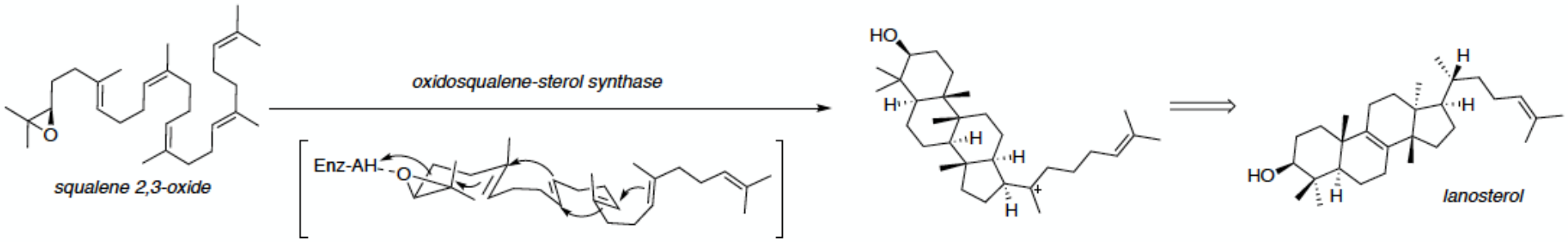
JOC **2021** 86 15433

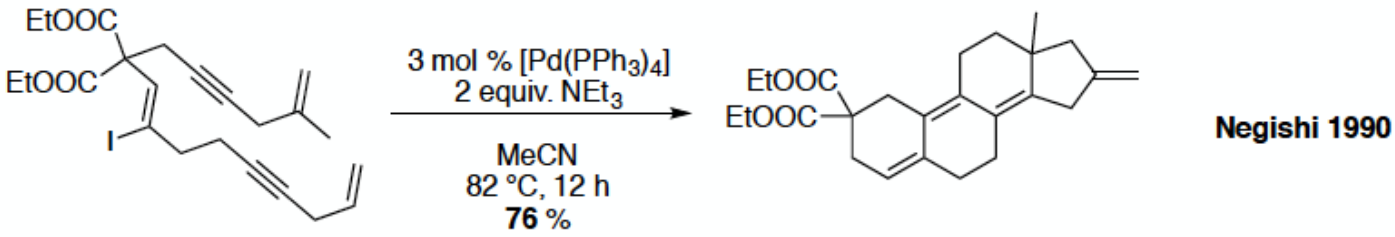
J Phys Chem A **2021** *125* 10035



TWO-PHOTON ACTIVATION OF REDOX INHERT STYRENES

HOW NATURE AND CHEMISTS CAN SEAL FOUR CYCLES IN A SEQUENCE

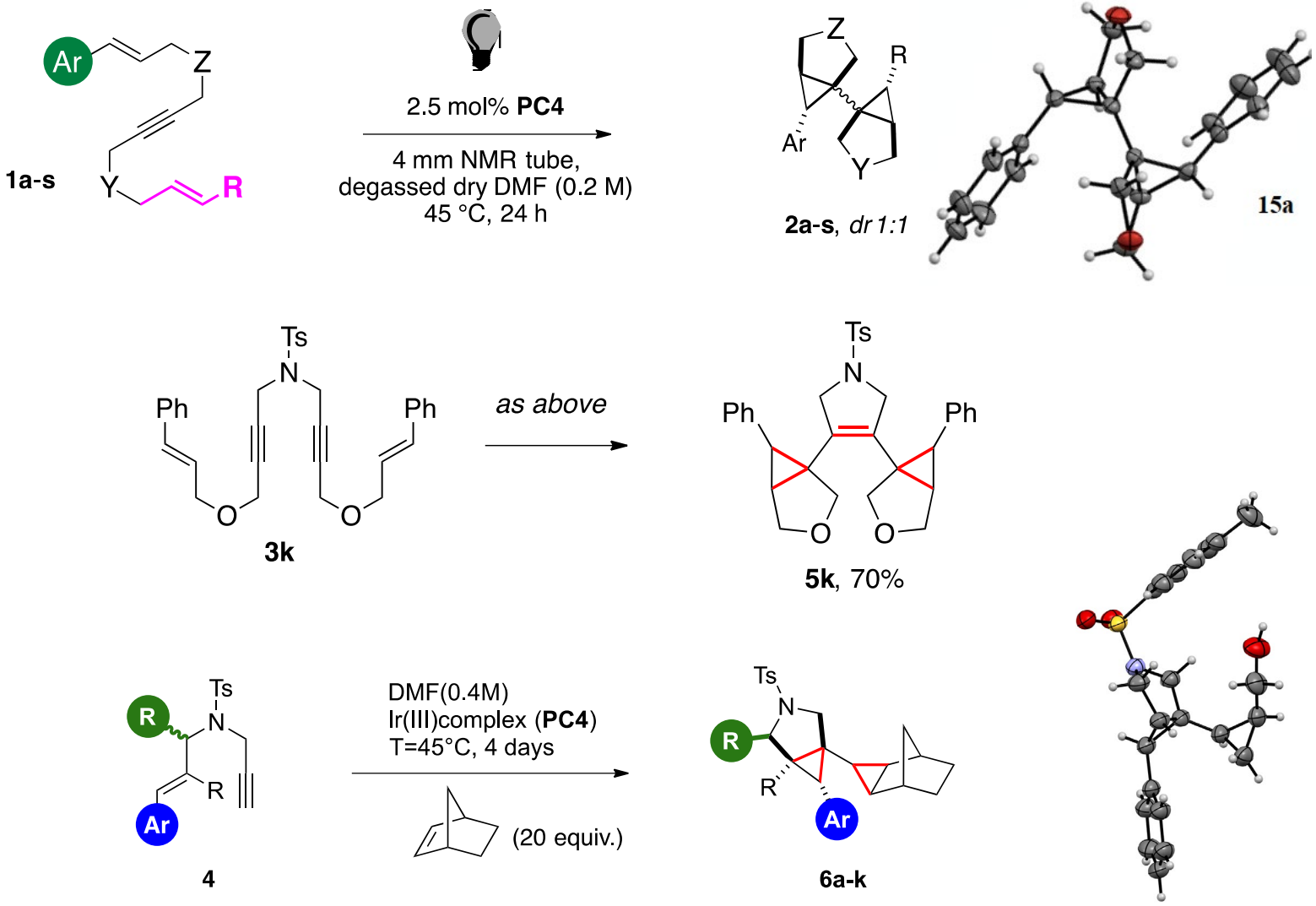




Negishi 1990

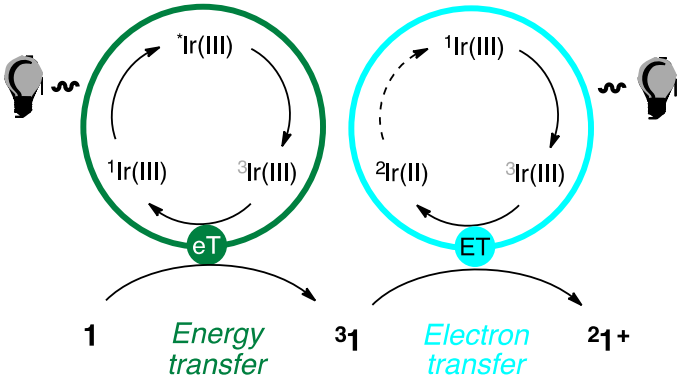
W. D. Nes *Chem. Rev.* **2011**, *111*, 6423; E. I. Negishi *J. Am. Chem. Soc.* **1990**, *112*, 8590

HIGHLIGHTING THE DICARBENOID BEHAVIOUR OF ALKYNES

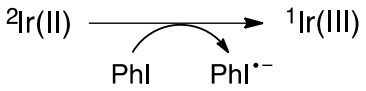


PROPOSED MECHANISM

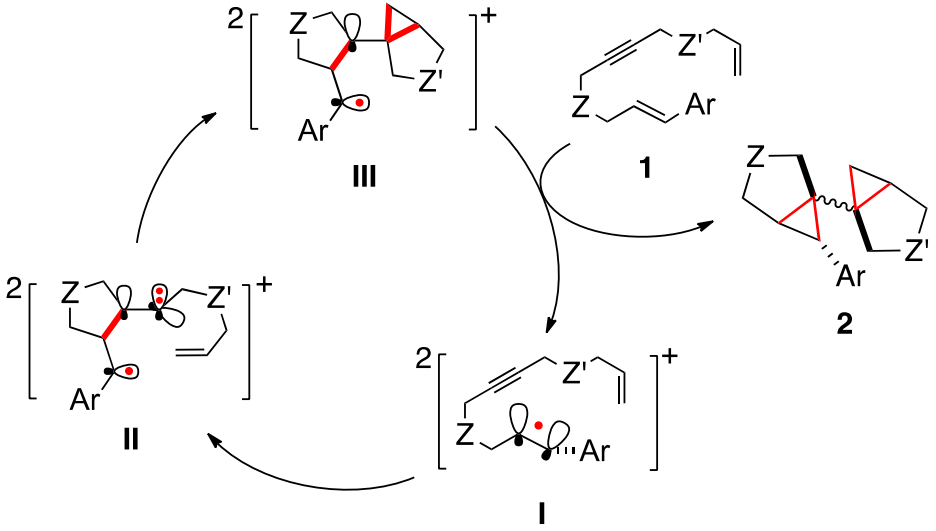
a) 2-photon initiation

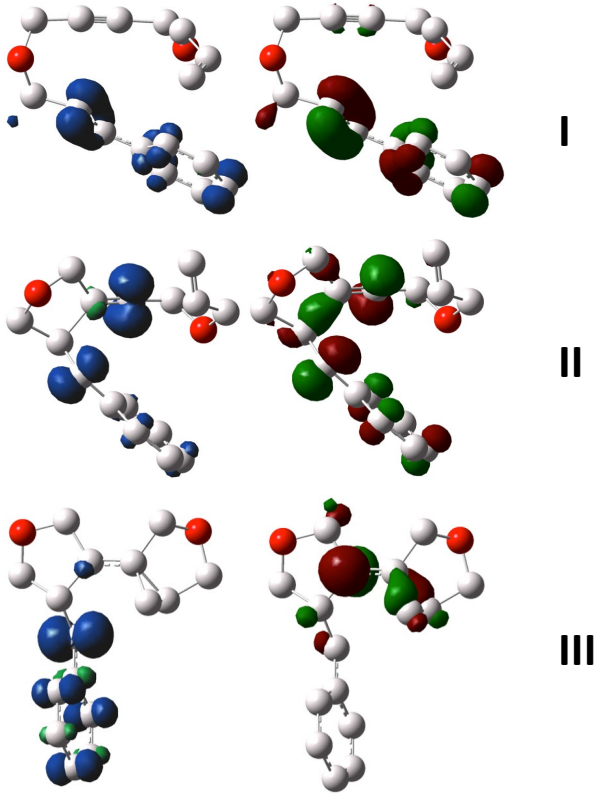


c) smart re-initiation

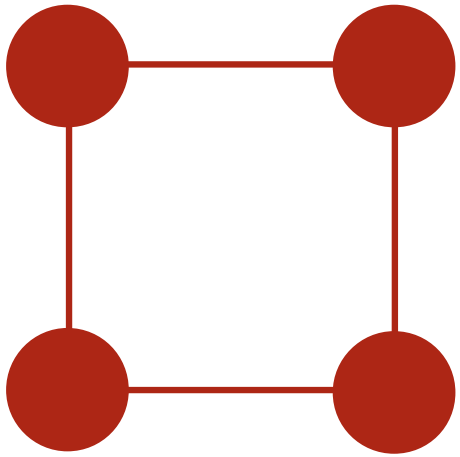


b) propagation



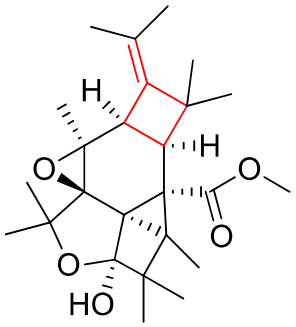


FOUR-MEMBERED RINGS

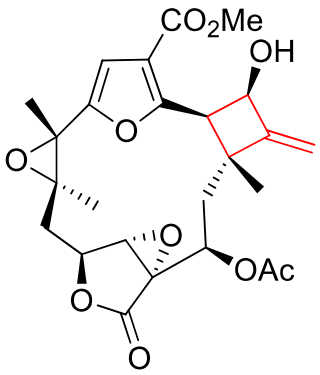


TUNING ALLENE DIFUNCTIONALIZATION

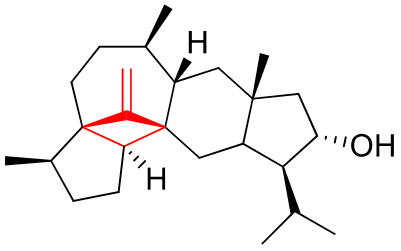
RELEVANT VINYLIDENE CYCLOBUTANES AND REGIOCHEMICAL ISSUES



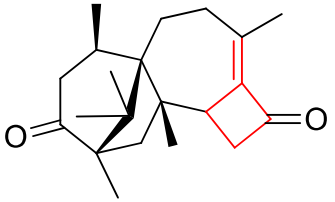
GLUTINOPALLAL



PROVIDENCIN

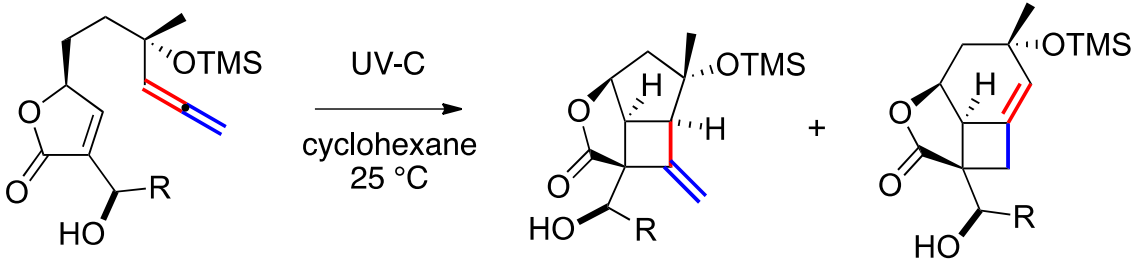


ASTELLATOL



HARZANDIONE

a) regiochemical issues in the [2+2] cycloaddition towards bielschowskysin



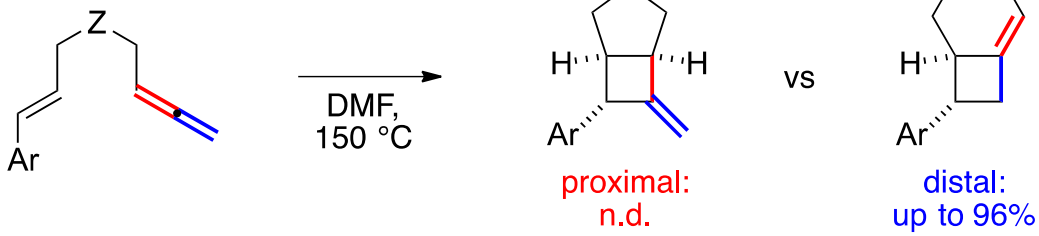
proximal / distal (undesired) ratio:
4.4 : 1

Tetrahedron Lett. **2009**, *50*, 1731

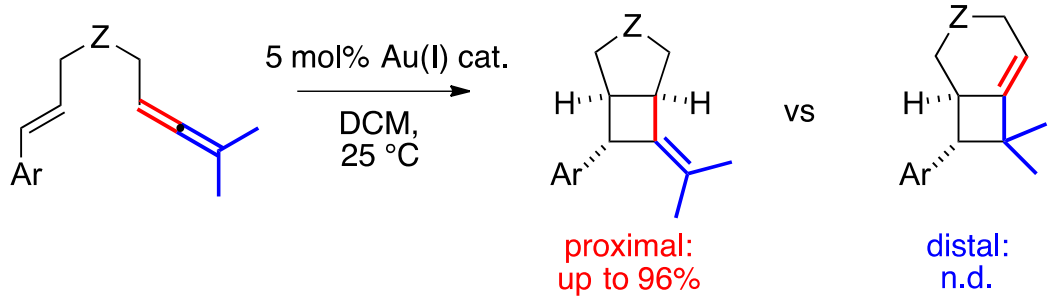
Bach *ChemRev* **2016**, *116*, 9748; Brown *ACIE* **2015**, *54*, 11918; Alcaide, Almendros *ChemSocRev* **2010**, *39*, 783

COMPLEMENTARY ROUTES TO SELECTIVE DIFUNCTIONALIZATION OF ALLENES

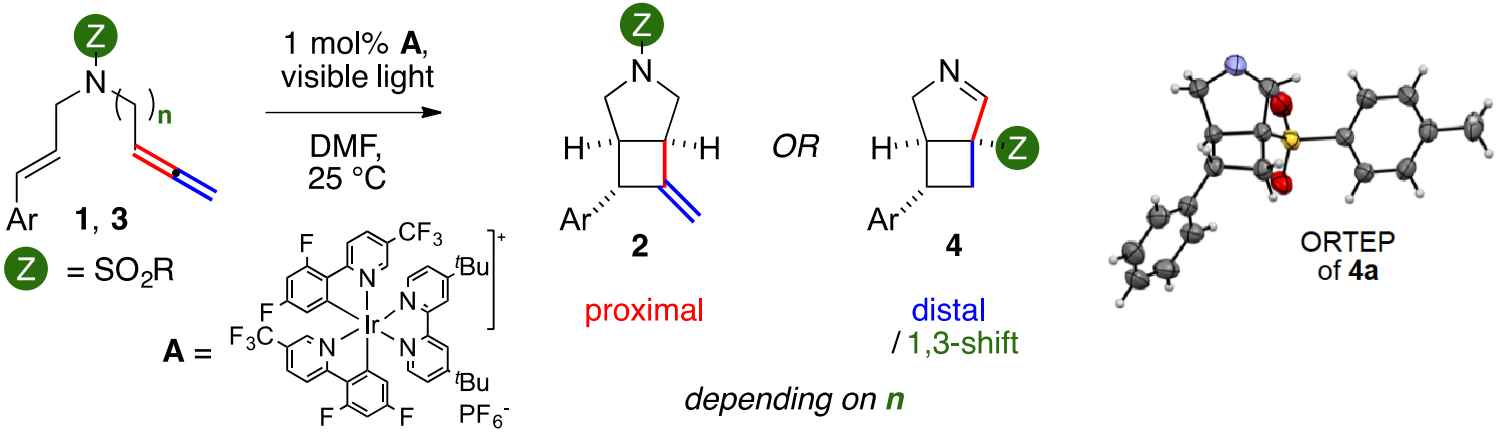
a) the thermal strategy



b) the metal-catalyzed allene activation strategy



c) present work: visible-light promoted ene activation

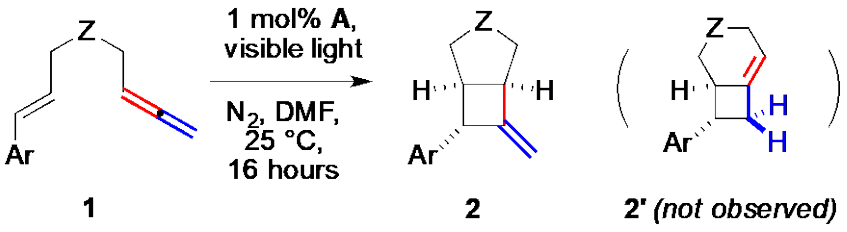


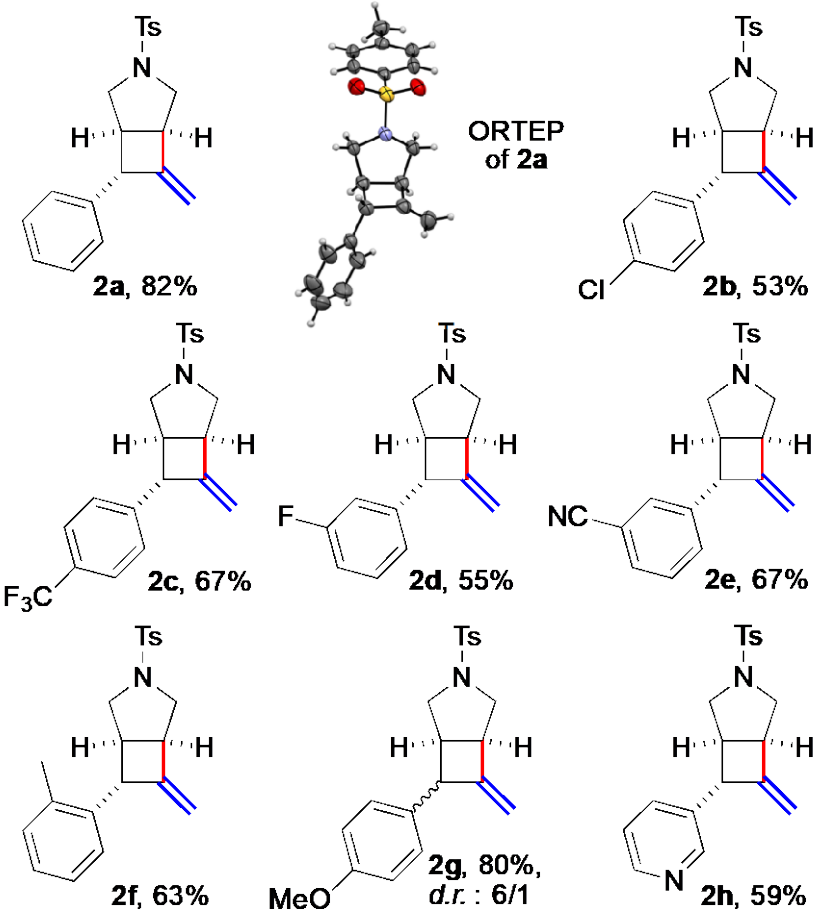
Thermal: Tanaka, *J. Org. Chem.* **2007**, *72*, 4378

Au: Toste, *J. Am. Chem. Soc.* **2007**, *129*, 12402

Our contribution: OL **2020**, 22, 6354

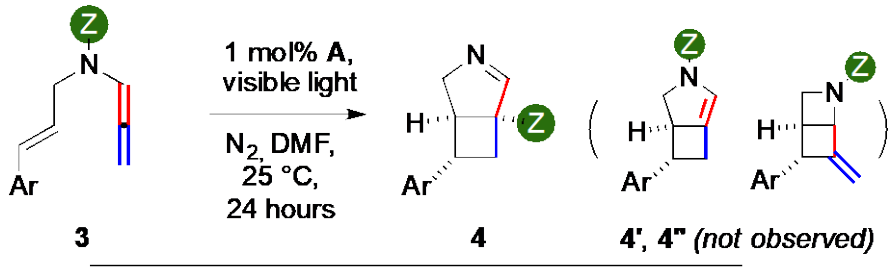
SELECTIVE PROXIMAL DIFUNCTIONALIZATION OF 1,7-ENALLENES



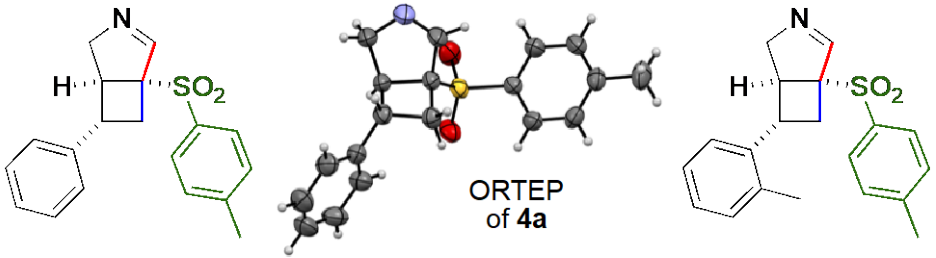


OL **2020**, 22, 6354

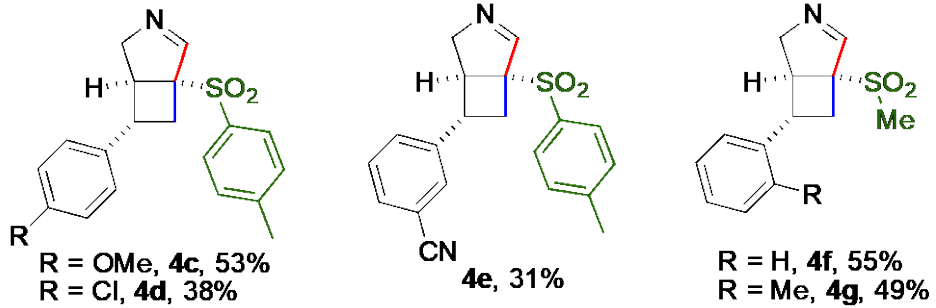
1,3-SULFONYL MIGRATION WITH 1,6-ENALLENES



3 **4** **4', 4" *(not observed)***



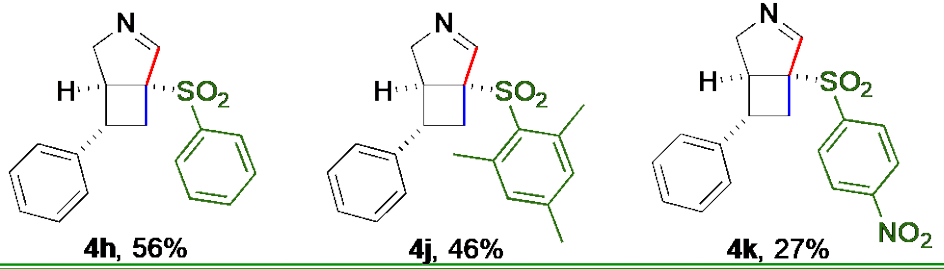
4a, 59% **4b**, 58%



R = OMe, **4c**, 53%
R = Cl, **4d**, 38%

4e, 31%

R = H, **4f**, 55%
R = Me, **4g**, 49%

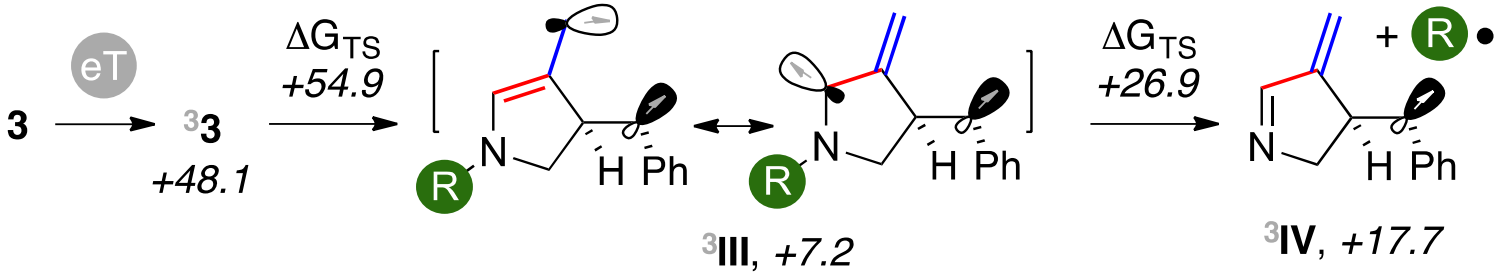


4h, 56% **4j**, 46% **4k**, 27%

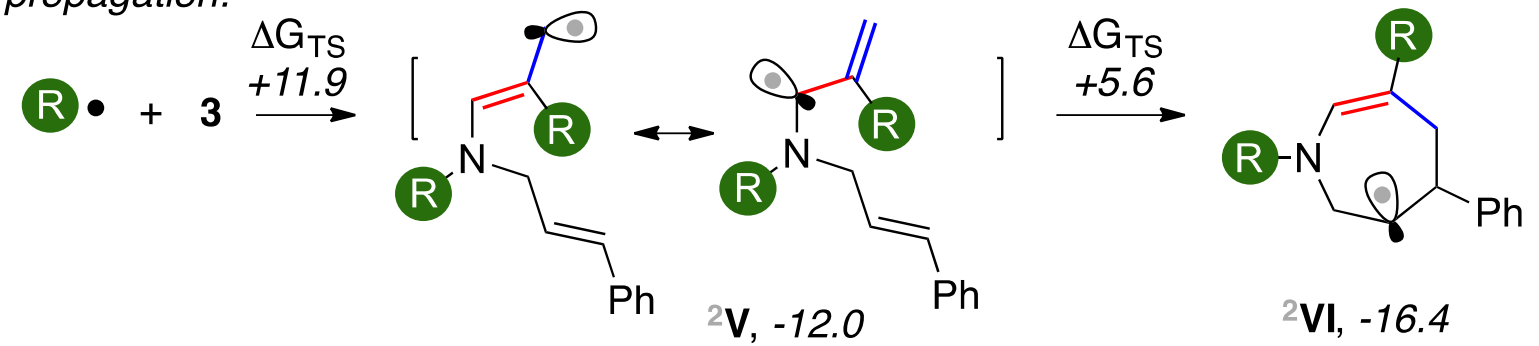
A RADICAL PROCESS PROMOTED BY VISIBLE LIGHT

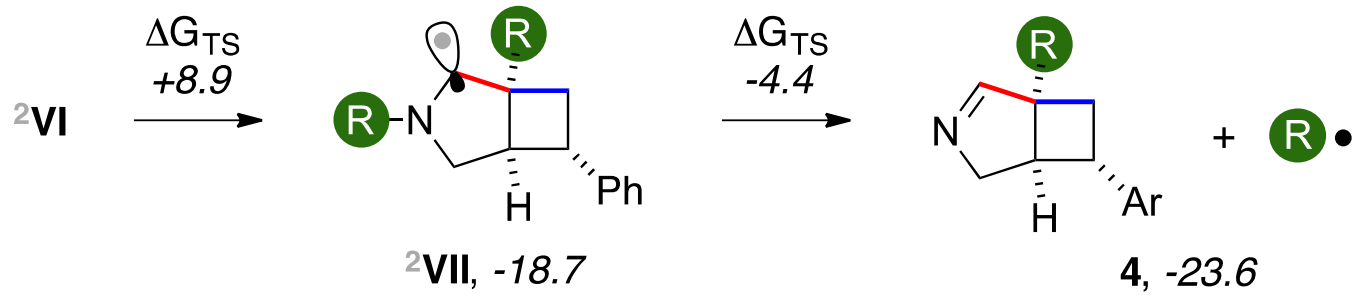
The radical chain of 1,6-allenenes

initiation:

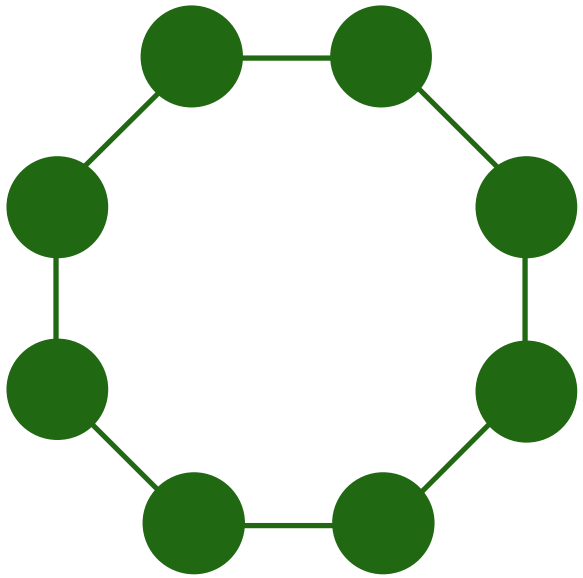


propagation:



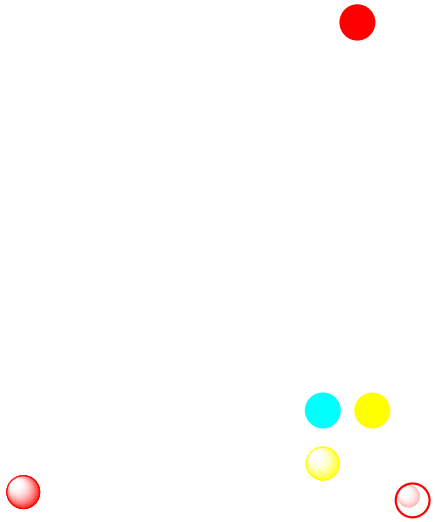


EIGHT-MEMBERED RINGS



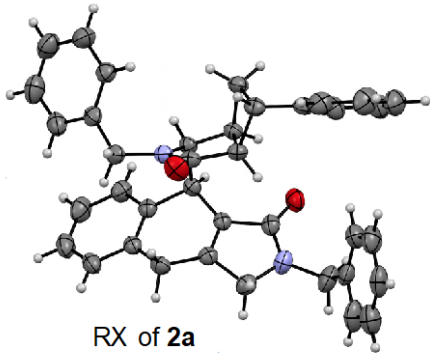
TUNING ALLENE DIFUNCTIONALIZATION (TWICE)

THE CYCLOBUTANE PARADIGM

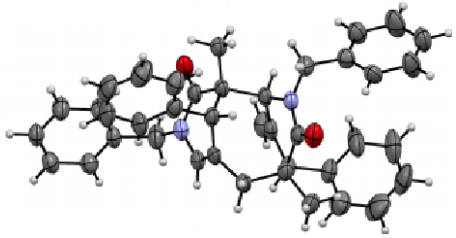


Bach *ChemRev* **2016**, *116*, 9748; Brown *ACIE* **2015**, *54*, 11918; Alcaide, Almendros *ChemSocRev* **2010**, *39*, 783

PARADIGMS ARE MEANT TO BE BROKEN…

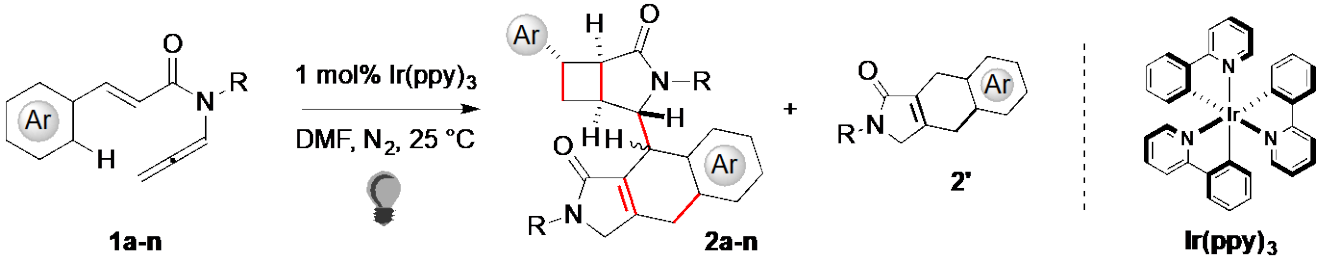


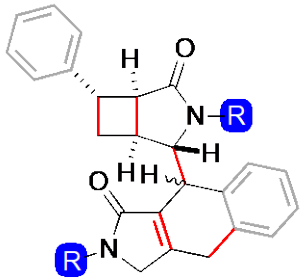
RX of **2a**



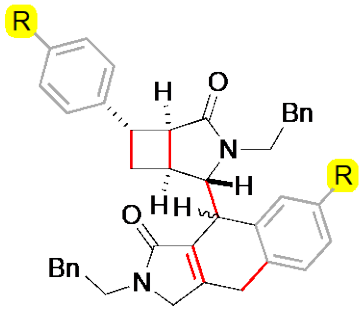
RX of **4a (dia 1)**

INTERMOLECULAR POLYCYCLIZATION OF ENALLENES

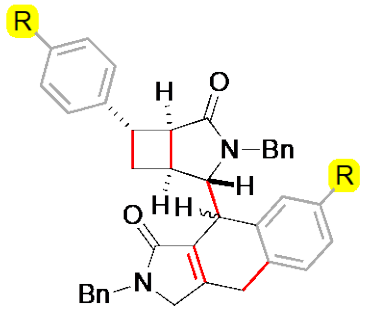




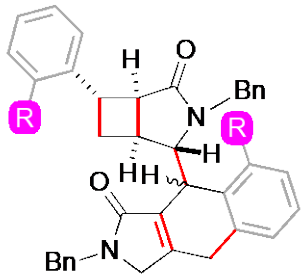
2a, R = CH_2Ph, 54%
2b, R = nC_9H_{19}, 36%
2c, R = CH_2CH_2Ph, 48%
2d, R = Ph, 17%
2e, R = cyclopropyl, 54%



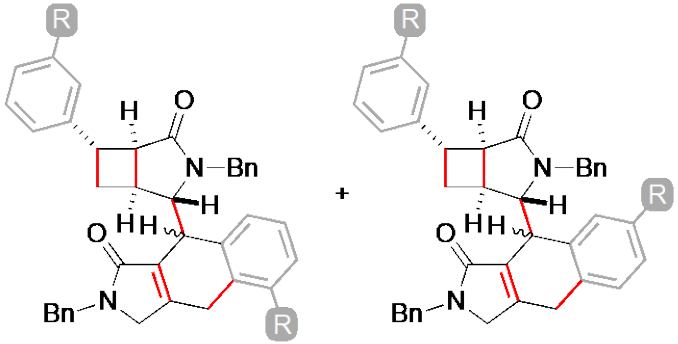
2f, R = Cl, 32%



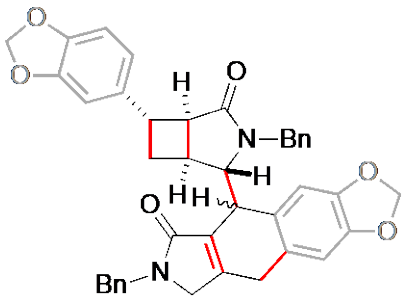
2g, R = Br, 44%
2h, R = OMe, 57%



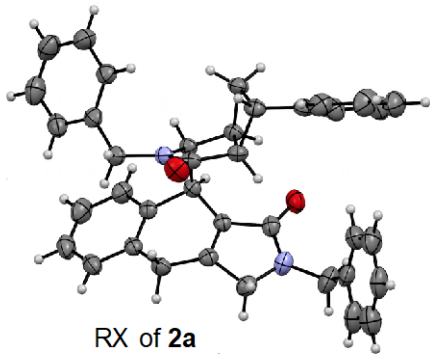
2i, R = Me, 60%



2j, R = Me, 54% (1:1)
2k, R = OMe, 63% (1:1)

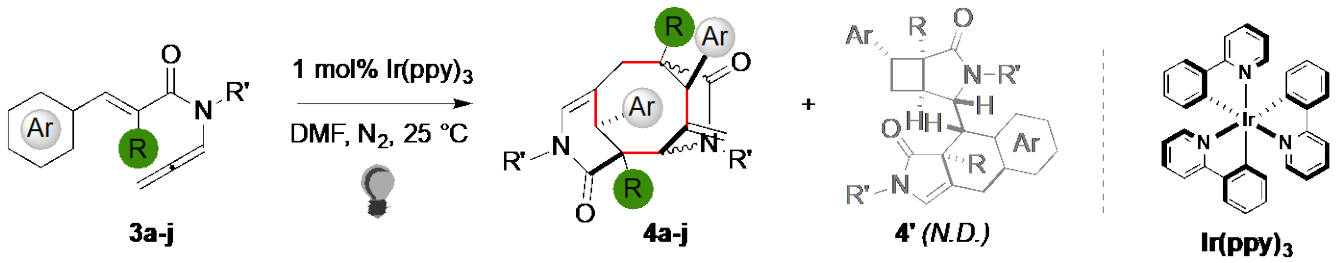


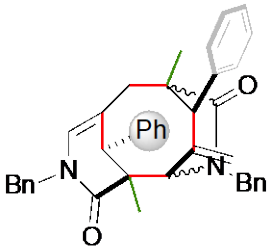
2n, 61%



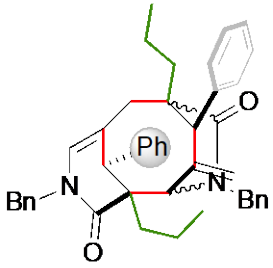
RX of **2a**

ACCESS TO TRICYCLIC CYCLOOCTANES

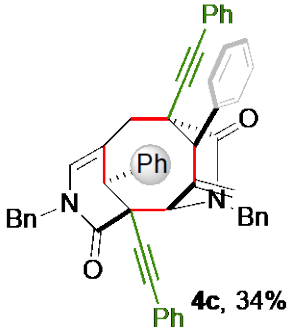




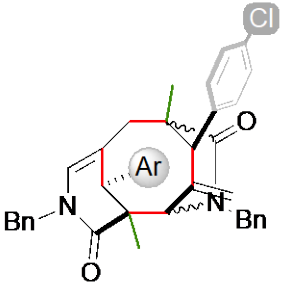
4a, 64%



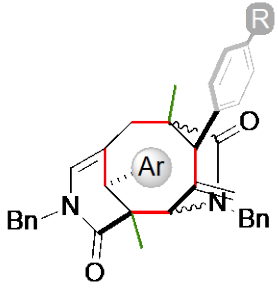
4b, 54%



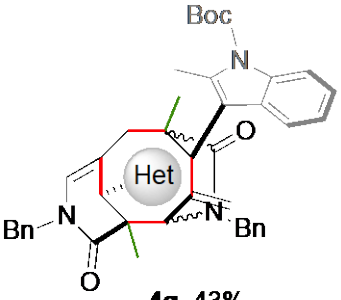
4c, 34%



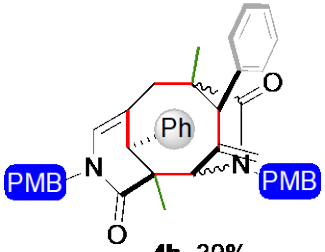
4d, 34%



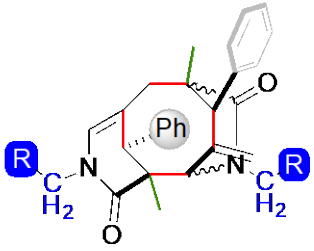
4e, R = OMe, 41%
4f, R = *n*Bu, 42%



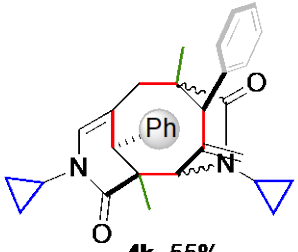
4g, 43%



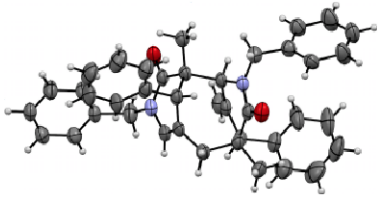
4h, 39%



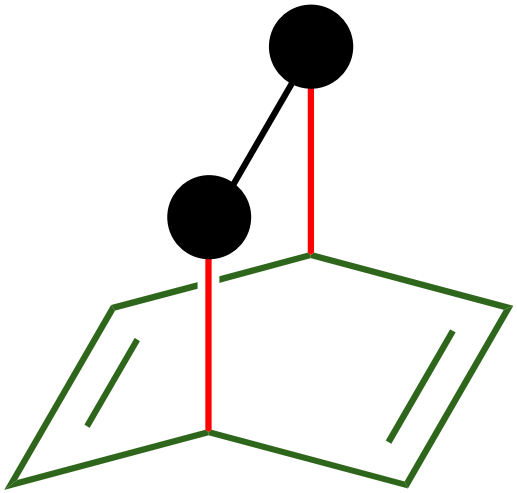
4i, R = 4-F-C_6H_4, 49%
4j, R = CN, 61%



4k, 55%



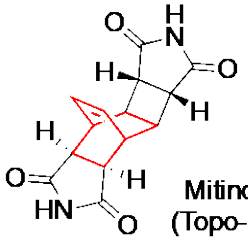
RX of **4a** (dia 1)



BREAKING AROMATICITY: A USEFUL ESCAPE FROM FLATLAND

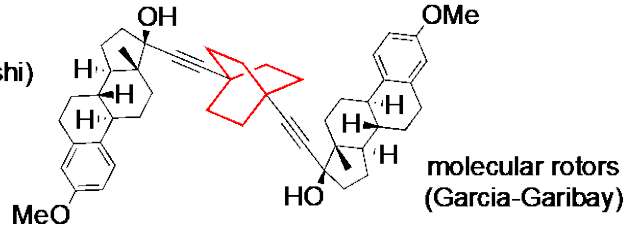
A DIFFICULT TASK…

Countless diversified targets



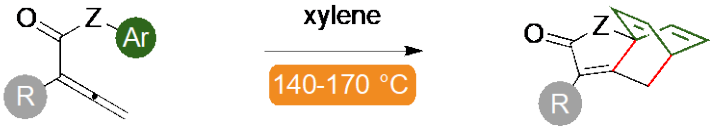
Mitindomide
(Topo-II inhib.)

chiral ligands
(Carreira, Hayashi)



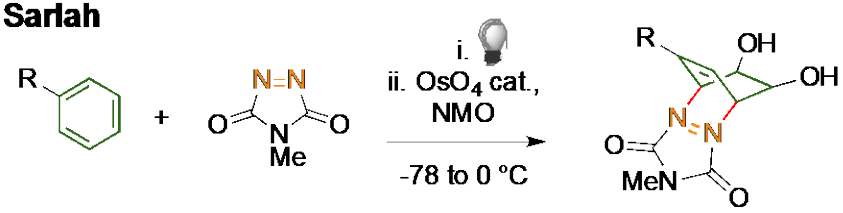
molecular rotors
(Garcia-Garibay)

Himbert



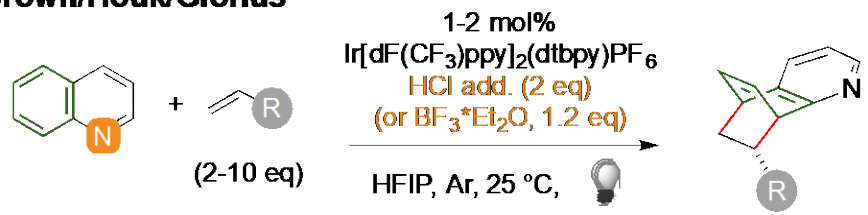
- conceptual breakthrough
- forcing conditions/scope

Sarlah



- simple, tunable
- unsuitable for bridged carbocycles

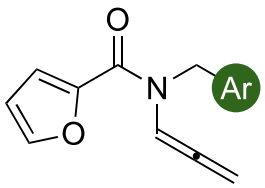
Brown/Houk/Glorius



- RT, intermolecular
- (iso)quinoline carbocycles, crucial acid additive

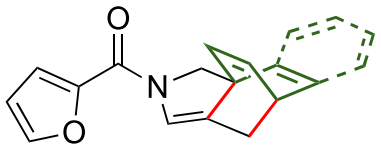
Himbert: ACIE ***1982*** *21* 620; *Sarlah: Nat Chem* ***2016*** *8* 922; *B&H&G: Science* ***2021*** *371* 1338

A CHALLENGING OPTIMIZATION



1aa, Ar = Ph
1a, Ar = 1-naphthyl

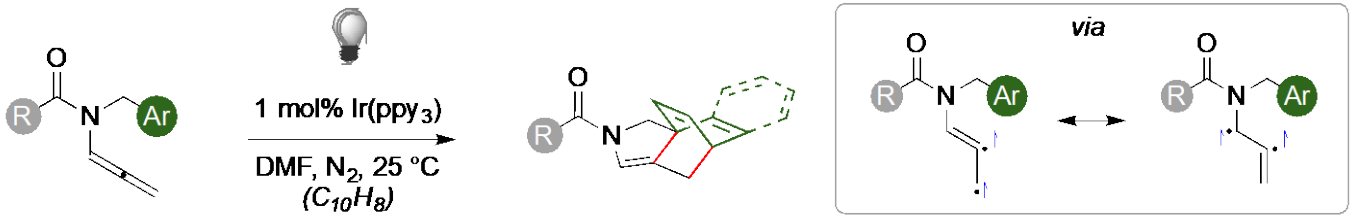
1 mol% sensitizer
DMF, N_2, 25 °C
additive, time



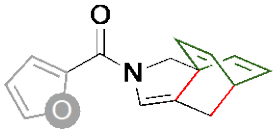
2

Reagent	Sensitizer	Additive (eq.)	Time (h)	Yield of **2** (%)
1aa	$Ir(ppy)_3$	--	240	46
1a	$Ir(ppy)_3$	--	3	99
1aa	$Ir(ppy)_3$	$C_{10}H_8$ (10)	48	60
1aa	$Ir(ppy)_3$	$C_{10}H_8$ (20)	38	64
1aa	$Ir(ppy)_3$	1-Methoxy-naphthalene (10)	24	70

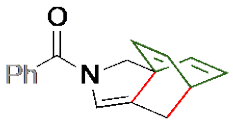
A SIMPLE METHOD SUITABLE FOR UNBIASED ARENES



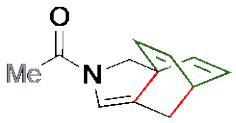
RT, dearomatization of simple aryls & pyridines, tolerant to -Br, -I, alkenes, alkynes, amines, epoxides, het-..



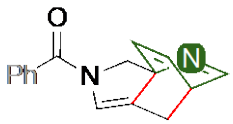
2aa, 65%



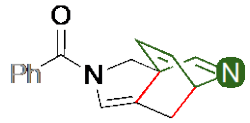
2ab, 75%,
62% on 2 mmol,
N.D. w/o $C_{10}H_8$



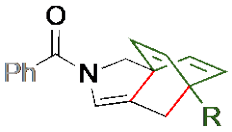
2ac, 56%



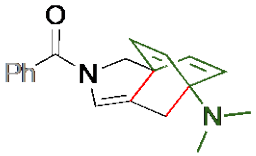
2aw, 61%



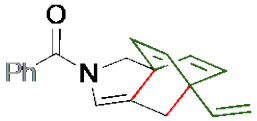
2ax, 56%



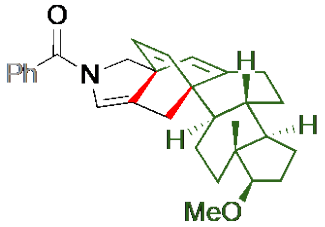
2ag, R = Me, 77%
2ah, R = OMe, 62%



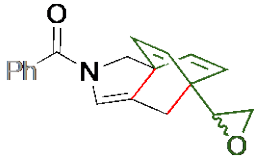
2ai, 54%



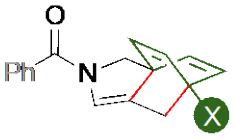
2aj, 41%



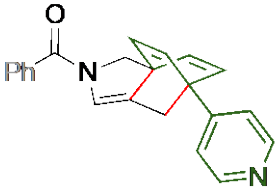
2av, 55%, *dr* = 69:31



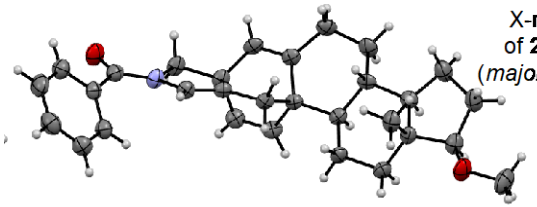
2ak, 76%, *dr* = 1:1



2al, X = F, 65%
2am, X = Br, 76%

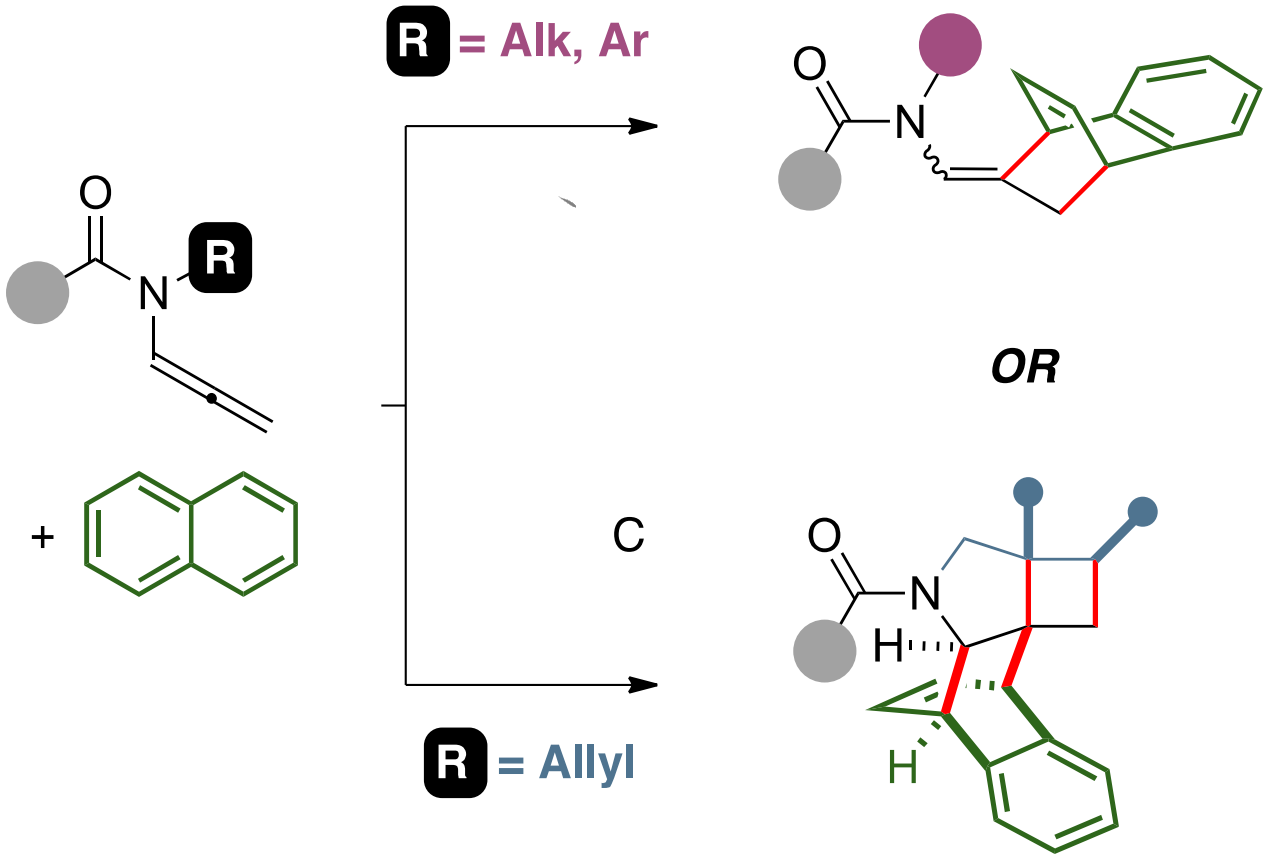


2an, 73%

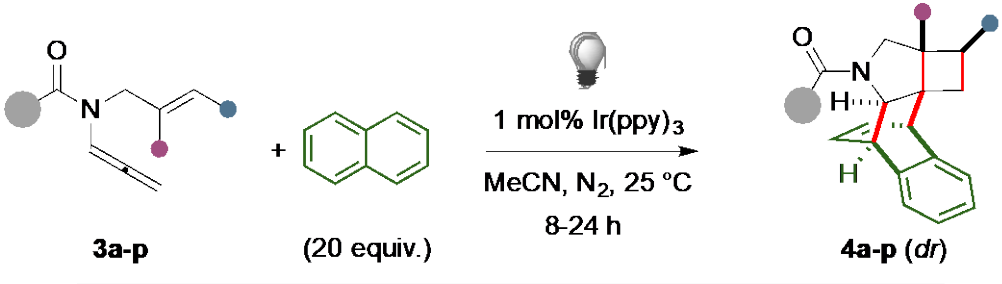


X-ray
of **2av**
(*major dia.*)

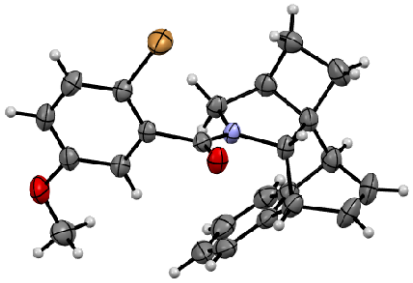
AN INTERMOLECULAR VARIANT



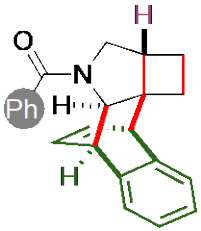
INTERMOLECULAR DEAROMATIZATION WITH ENALLENES



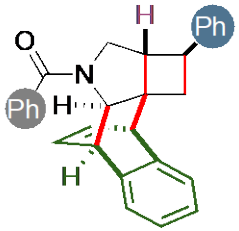
3a-p (20 equiv.) **4a-p** (*dr*)



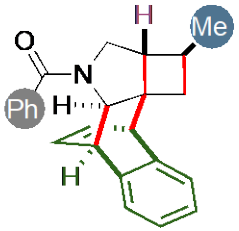
X-ray of **4h**, *major dia*



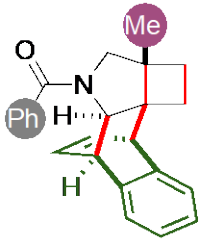
4a, 76%, *70:30*, 60% on 1 mmol



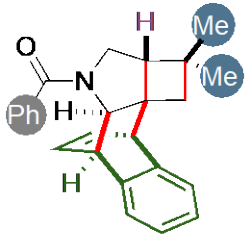
4b, 45%, *74:26*



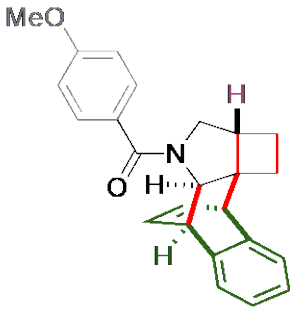
4c, 61%, *71:29*



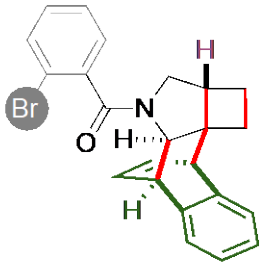
4d, 44%, *71:29*



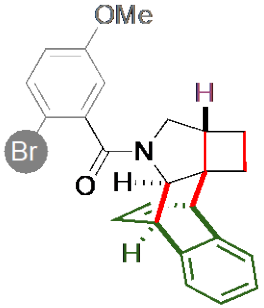
4e, 79%, *74:26*



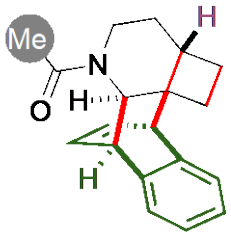
4f, 73%, *67:33*



4g, 62%, *73:27*

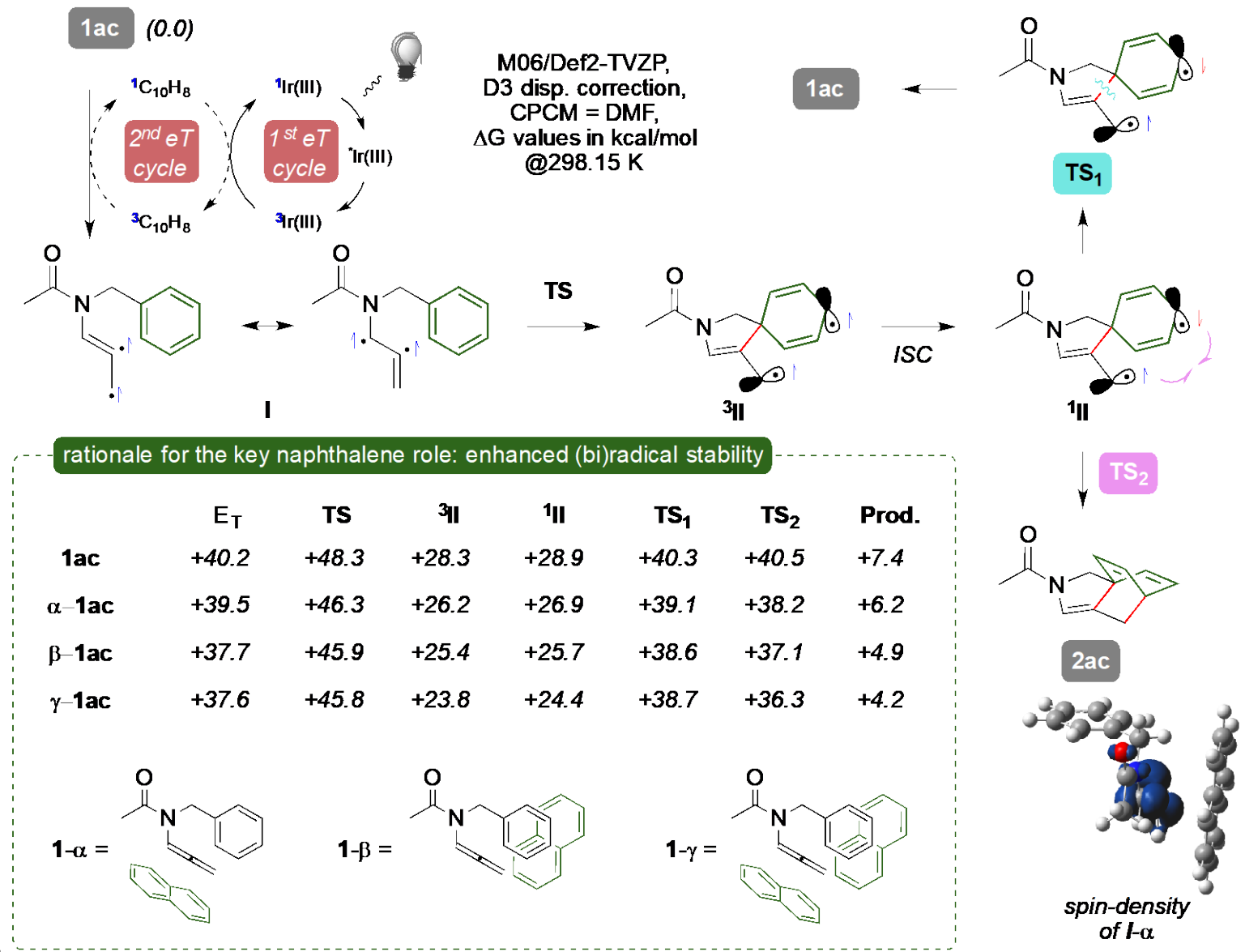


4h, 60%, *75:25*



4m, 45%

THE BENEFICIAL ROLE OF NAPHTHALENE



rationale for the key naphthalene role: enhanced (bi)radical stability

	E_T	TS	^{3}II	^{1}II	TS_1	TS_2	Prod.
1ac	*+40.2*	*+48.3*	*+28.3*	*+28.9*	*+40.3*	*+40.5*	*+7.4*
α–**1ac**	*+39.5*	*+46.3*	*+26.2*	*+26.9*	*+39.1*	*+38.2*	*+6.2*
β–**1ac**	*+37.7*	*+45.9*	*+25.4*	*+25.7*	*+38.6*	*+37.1*	*+4.9*
γ–**1ac**	*+37.6*	*+45.8*	*+23.8*	*+24.4*	*+38.7*	*+36.3*	*+4.2*

1-α =

1-β =

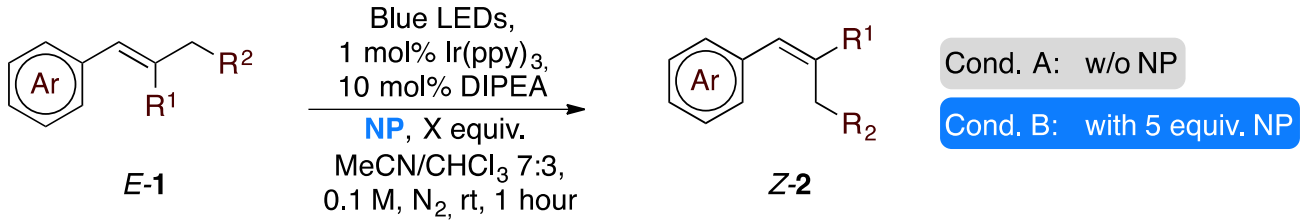
1-γ =

CAN WE PLAY WITH DISPERSION INTERACTIONS?

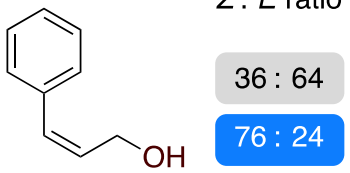
The seminal work:

Facile Synthesis of *Z*-Alkenes via Uphill Catalysis

by Weaver, *JACS* **2014**, *136*, 5275



a) **Substrate variation**

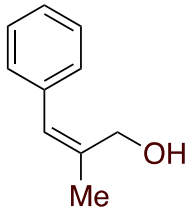


Z-**2a**

Z: *E* ratio

36 : 64

76 : 24

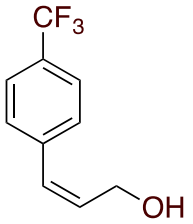


Z-**2b**

Z: *E* ratio

6 : 94

41 : 59

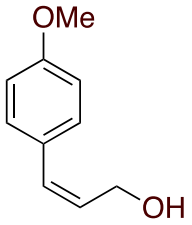


Z-**2c**

Z: *E* ratio

39 : 61

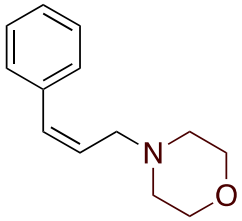
60 : 40



Z-**2d**

61 : 39

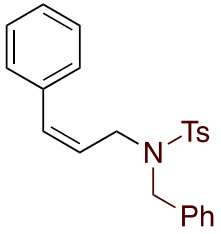
76 : 24



Z-**2e**

30 : 70

81 : 19

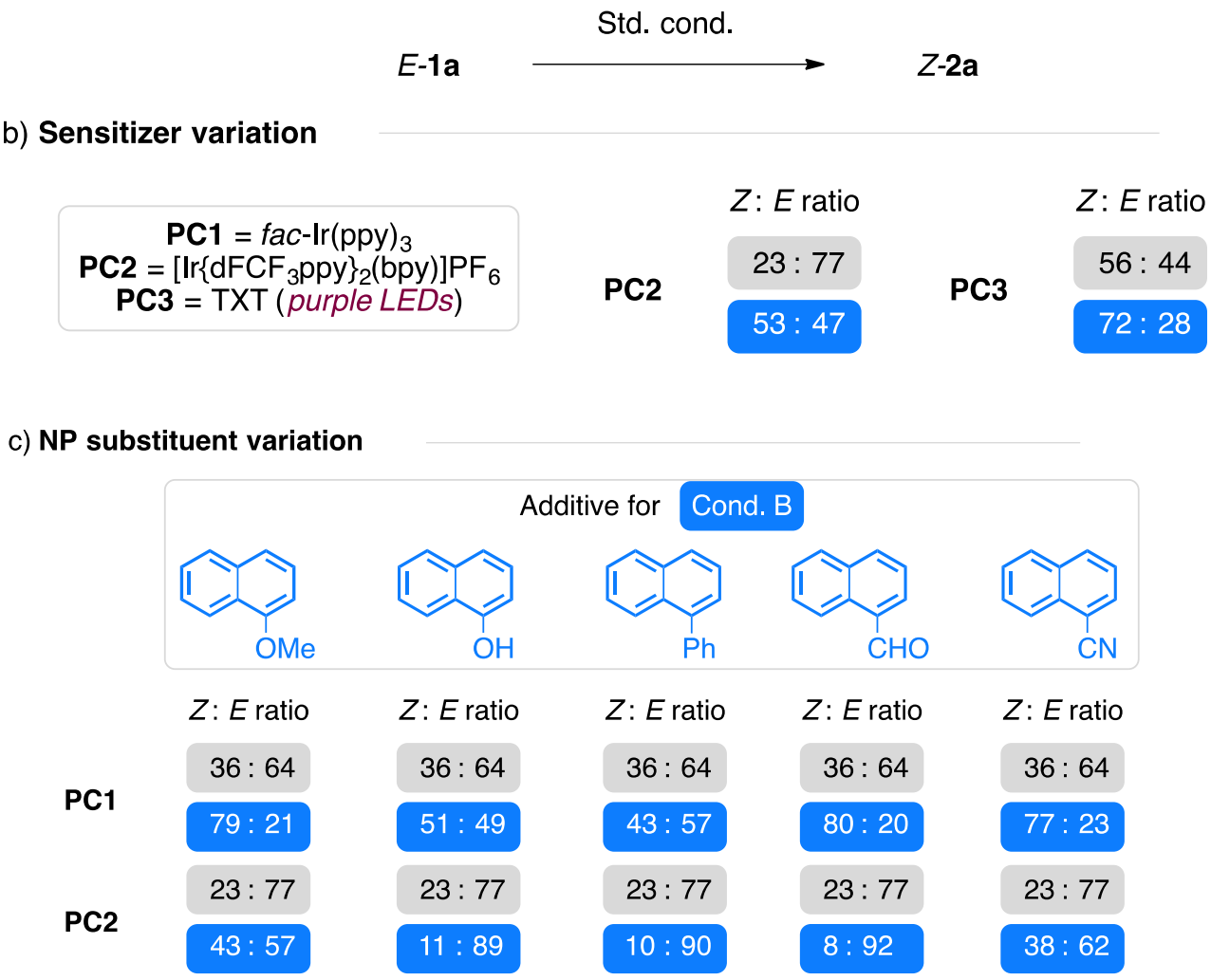


Z-**2f**

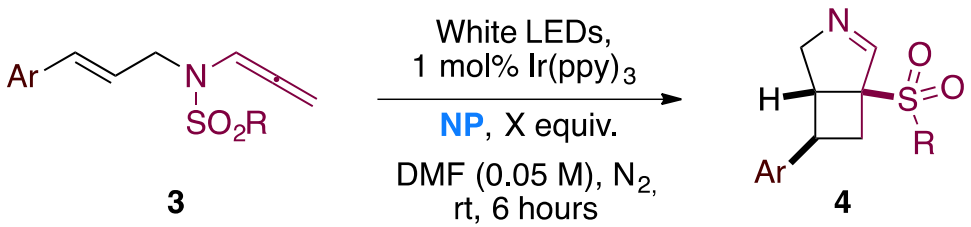
36 : 64

88 : 12

THE GENERALITY OF THE EFFECT

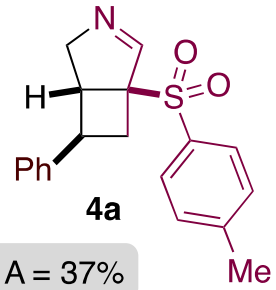


A SULFONYL- RADICAL CHAIN



Cond. A: w/o NP

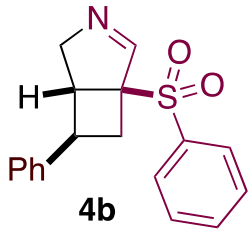
Cond. B: with 20 equiv. NP



4a

A = 37%

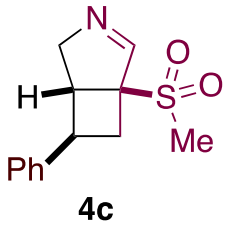
C = 48%



4b

A = 29%

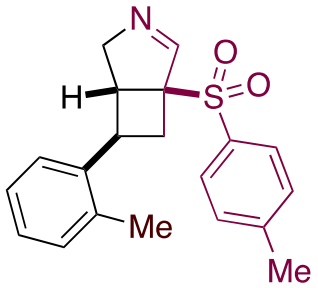
C = 55%



4c

A = 36%

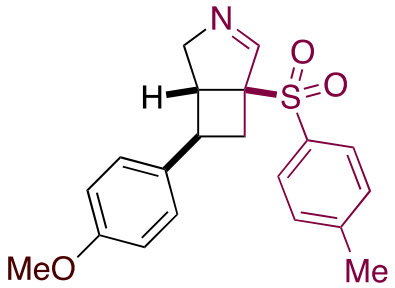
C = 60%



4d

A = 53%

C = 68%



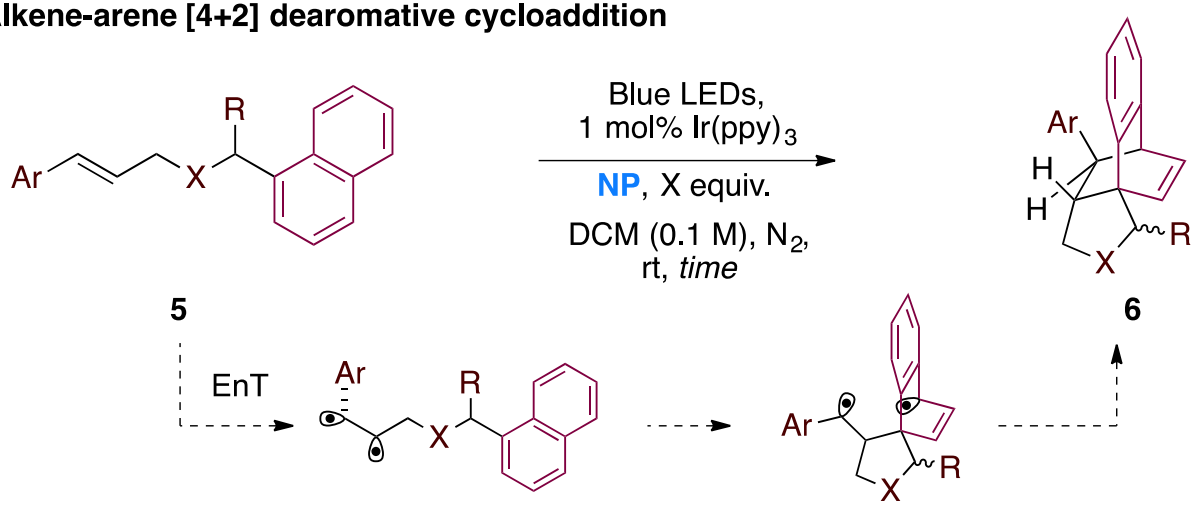
4e

A = 46%

C = 55%

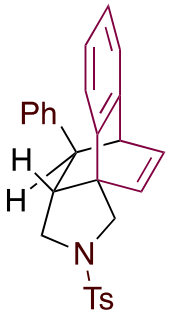
DEAROMATIZATION WITH ALKENES

Alkene-arene [4+2] dearomative cycloaddition



Cond. A: w/o NP

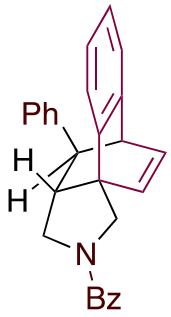
Cond. B: with 20 equiv. NP



6a, *dr* = 80:20

A = 94%, 8 h

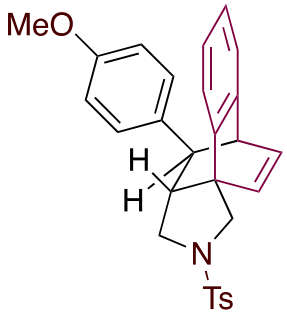
C = 95%, 2 h



6b, *dr* = 80:20

A = 94%, 10 h

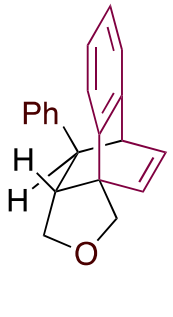
C = 93%, 3 h



6c, *dr* = 77:23

A = 92%, 3 h

C = 93%, 1 h

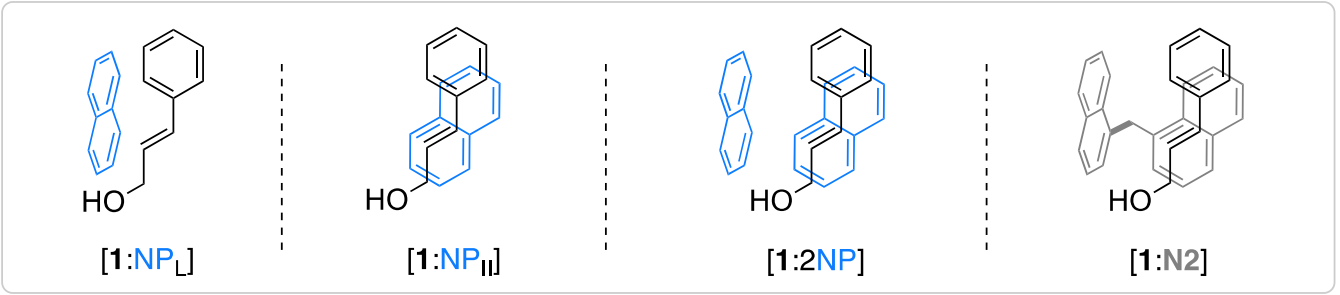


6d, *dr* = 84:16

A = 83%, 24 h

C = 93%, 5 h

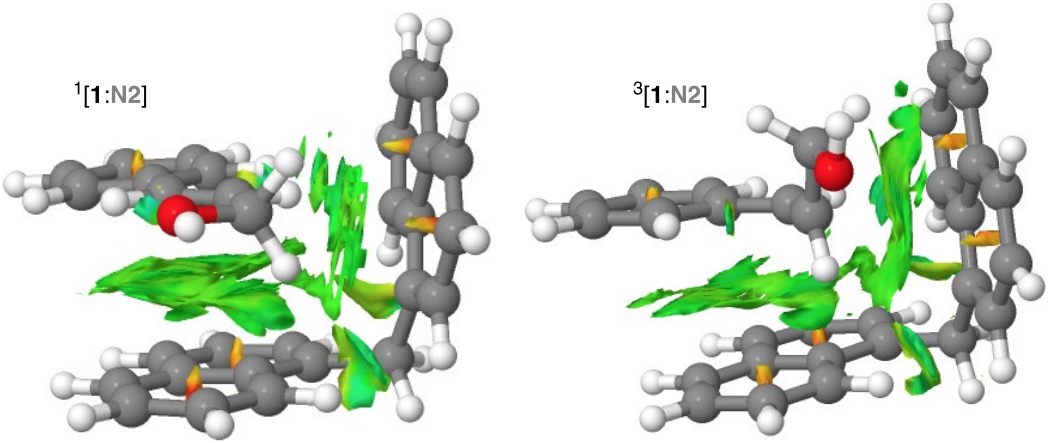
THE BALANCE BETWEEN ENTHALPY AND ENTHROPY



[**1**:NP_L] [**1**:NP_{II}] [**1**:2NP] [**1**:N2]

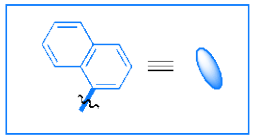
		singlets		triplets
	ΔH	ΔG	ΔG
1	*+0.0*	+0.0	+48.7
[**1**:NP_L]	*-8.3*	+2.6	+49.9
[**1**:NP_{II}]	*-7.1*	+3.2	+51.8
[**1**:2NP]	*-19.2*	+1.6	+51.2
[**1**:N2]	***-13.8***	**-2.0**	**+45.6**

kcal/mol values @298.15 K, M06/Def2-TZVP, Grimme's D3 disp. corr., CPCM = MeCN

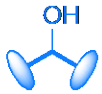


THE POWERFUL MULTIVALENT EFFECT

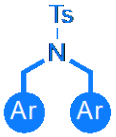
Poly-NP library



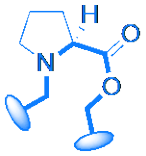
N1 (n = 0)
N2 (n = 1)



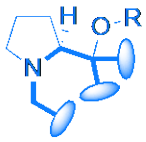
N3



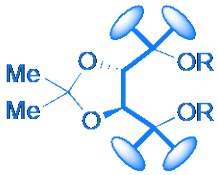
N4 (Ar = 1-$C_{10}H_7$)
N5 (Ar = 2-$C_{10}H_7$)



N6

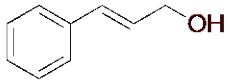


N7 (R = H)
N8 (R = TBDMS)



N9 (R = H)
N10 (R = Me)

a) Alkene isomerization

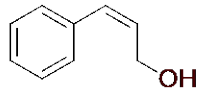


E-**1a**

Std. cond. (*Fig. 1*)

rt, 1 hour

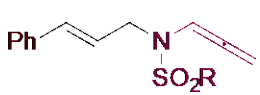
10 mol% N



Z-**2a**

w/o N, *Z*/*E* = 36:64	**N3**, *Z*/*E* = 61:39	**N7**, *Z*/*E* = 57:43
NP, *Z*/*E* = 43:57	**N4**, *Z*/*E* = 65:35	**N8**, *Z*/*E* = 51:49
N1, *Z*/*E* = 55:45	**N5**, *Z*/*E* = 47:53	**N9**, *Z*/*E* = 68:32
N2, *Z*/*E* = 55:45	**N6**, *Z*/*E* = 55:45	**N10**, *Z*/*E* = 63:37

b) Sulfonyl- radical chain

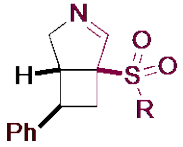


3

Std. cond. (*Fig. 2*)

rt, 6 h

20 mol% N4

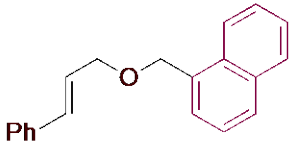


4

w/o N, **4b** = 29%, **4c** = 36%

4b = 51%, **4c** = 56%

c) Alkene-arene dearomative [4+2] cycloaddition

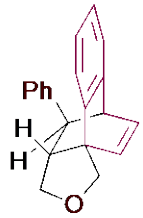


5d

Std. cond. (*Fig. 3*)

rt, *time*

1 equiv. N10

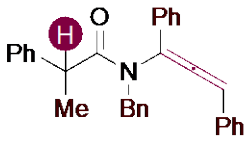


6d

w/o N, **6d** = 83%, *24 h* (*dr = 85:15*)

6d = 95%, *10 h* (*dr = 82:18*)

d) [1,5]-HAT/cyclization on allenamides

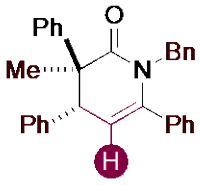


7c

Std. cond. (*Fig. 4*)

rt, 48 h

30 mol% N9

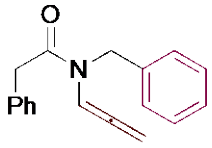


8c

w/o N, **8c** = *ND*

8c = 66% (*dr = 56:44*)

e) Allene-arene dearomative [4+2] cycloaddition

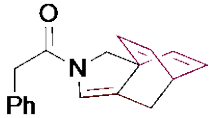


9a

White LEDs,
1 mol% $Ir(ppy)_3$

DMF (0.1 M), N_2,
rt, 48 h

30 mol% N4

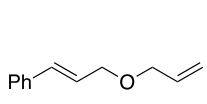


10a

w/o N, **10a** = 15%

10a = 79%

A BOOST FOR CHALLENGING [2+2]

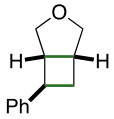


1a

Blue LEDs
1 mol% $Ir(ppy)_3$

A = no additive

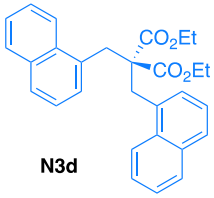
B = **N3d** 30 mol%



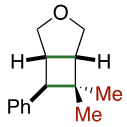
2a, *4 hrs*

A = 34%, 85:15 d.r.

B = 97%, 86:14 d.r.



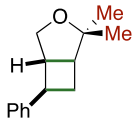
N3d



2b, *4 hrs*

A = 53%, 97:3 d.r.

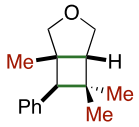
B = 86%, 97:3 d.r.



2c, *4 hrs*

A = 55%, 88:12 d.r.

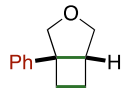
B = 99%, 88:12 d.r.



2d, *30 hrs*

A = 51%, 57:43 d.r.

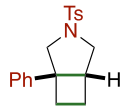
B = 96%, 57:43 d.r.



2f, *55 hrs*

A = 19% (30% at 92 hrs)

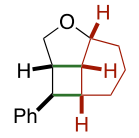
B = 56%



2g, *20 hrs*

A = 52%

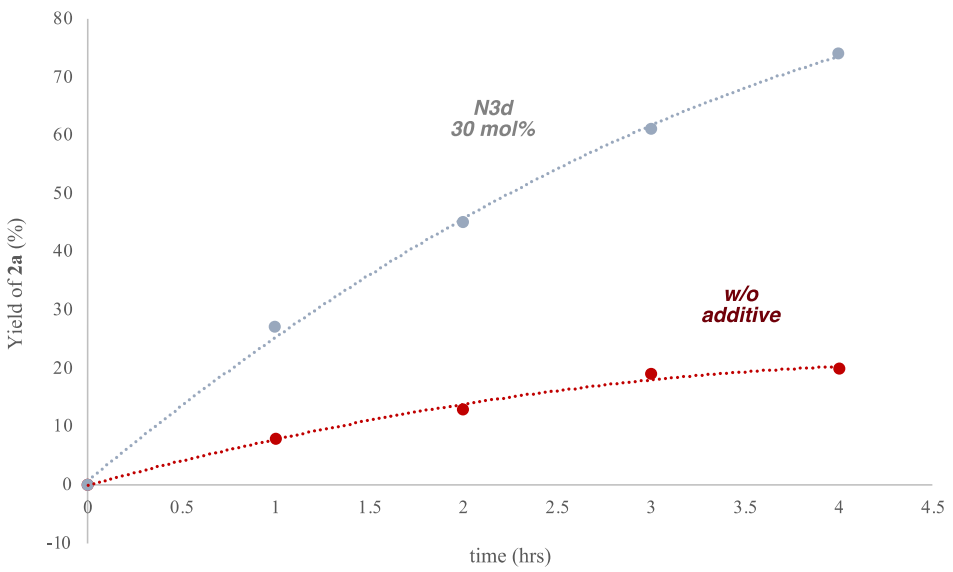
B = 80%



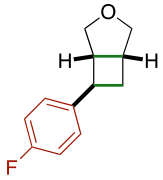
2h, *7 hrs*

A = 41%, 93:7 d.r.

B = 90%, 93:7 d.r.



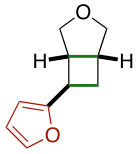
from piperonal



2j, *4 hrs*

A = 35%, 86:14 d.r.

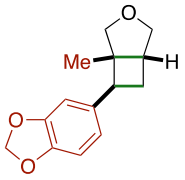
B = 93%, 85:15 d.r.



2k, *1 hrs*

A = 70%, 85:15 d.r.

B = 70%, 85:15 d.r.

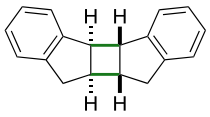


2l, *9 hrs*

A = 72%, 75:25 d.r.

B = 99%, 75:25 d.r.

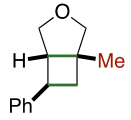
intermolecular [2+2]



2m, *72 hrs*

A = 27%

B = 70%

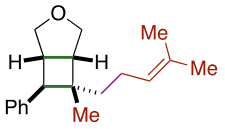


2e, *40 hrs*

A = 12%, 85:15 d.r.

B = 76%, 85:15 d.r.

from geraniol

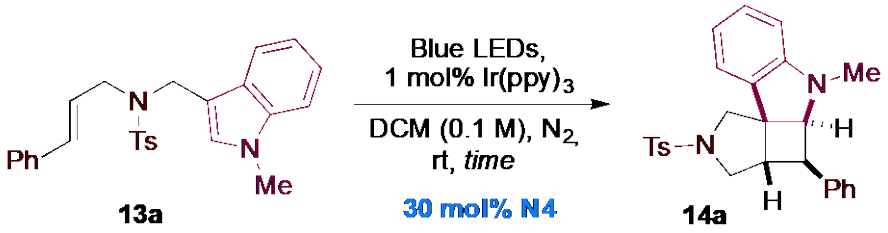


2i, *30 hrs*

A = 43%, 58:42 d.r.

B = 86%, 59:41 d.r.

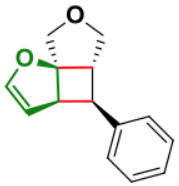
ALKENE-HETEROARENE DEAROMATIVE [2+2]



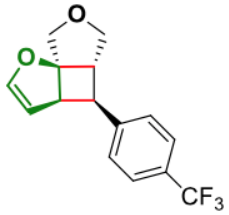
w/o N, **14a** = 37%, *24 h (dr = 99:1)*

14a = 77%, *6 h (dr = 99:1)*

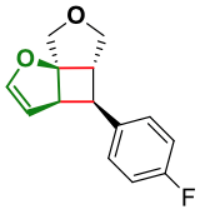
SIMPLE HETEROCYCLES



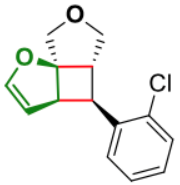
2a. 85%



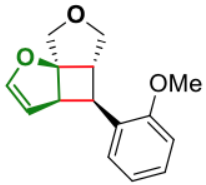
2b. 75%



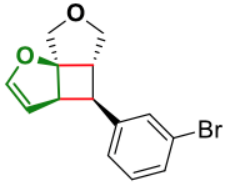
2c. 70%



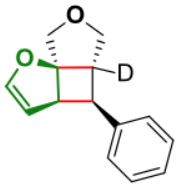
2d. 88%



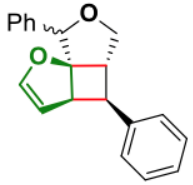
2e. 62%



2f. 84%

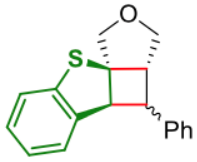


2g. 71%

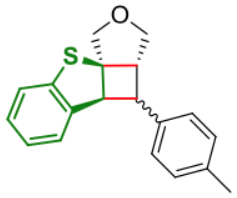


2h. 70%

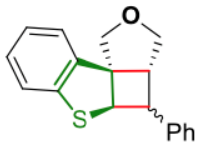
BENZOHETEROCYCLES



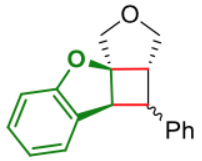
4a.[a] 99% (75:25)



4b.[a] 99% (75:25)

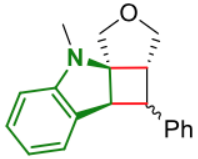


4c.[a] 92% (79:21)



4d.[a] 93% (86:14)

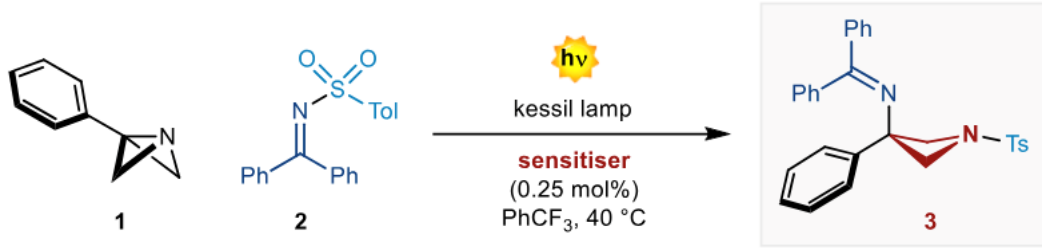
N-METHYL BENZOHETEROCYCLES



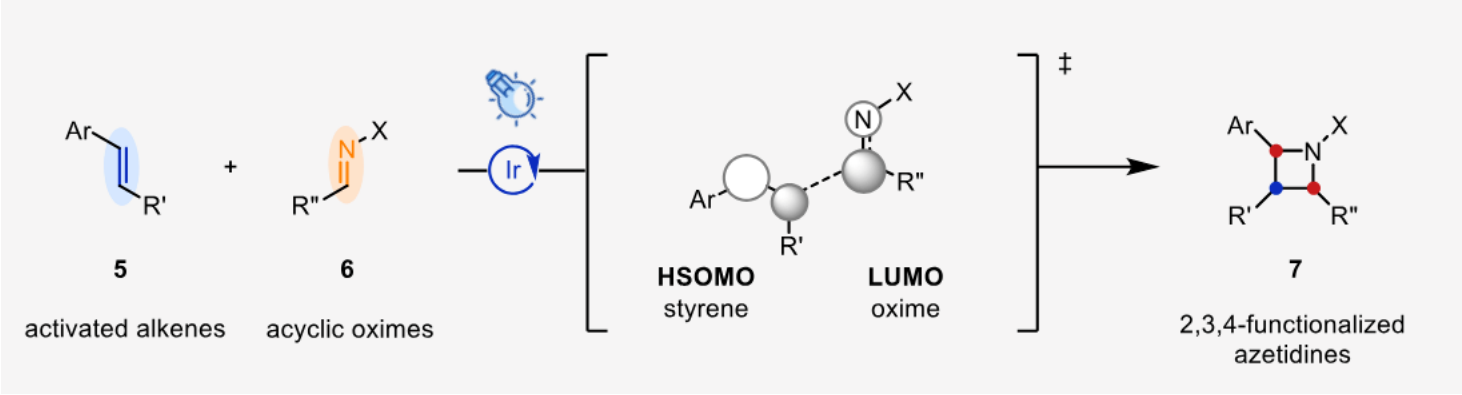
4e.[b] 89% (71:29)

TRACKING STRAINED 4-MEMBERED N- HETEROCYCLES

THE RECENT BACKGROUND



Dell'Amico *Nat. Catal.* **2024** *doi:* 10.1038/s41929-024-01206-4



Schindler *Science* **2024** *384* 1468

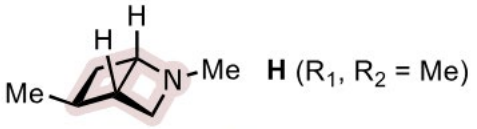
SYNTHESIS OF AZETIDINES VIA 1,5-HAT

Deviation from initial conditions	time (h)[b]	Yield of **3a** (%)[c]
PC1, no **N** co-cat	168	22
N4, **PC2**	84	52
N4, **PC5**, purple LEDs	24	76

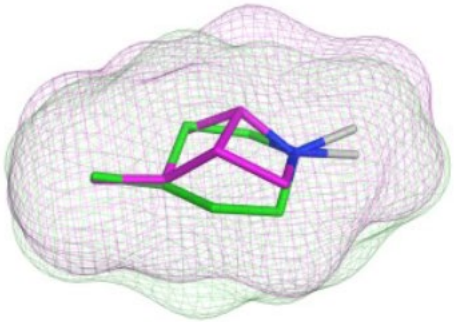
ASSEMBLY OF BETA-LACTAMS

THE CO-CATALYTIC EFFECT

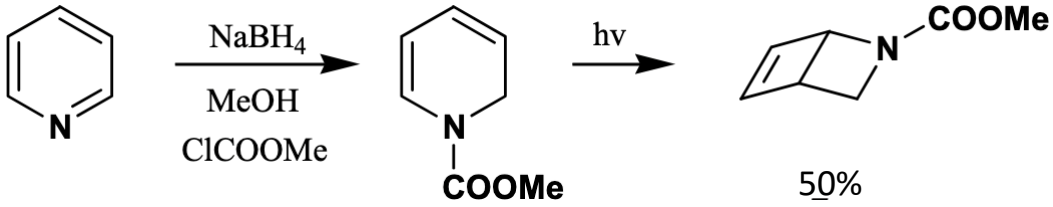
CAN WE TARGET PYRIDINE & PIPERIDINE BIO-ISOSTERES?



H (R_1, R_2 = Me)

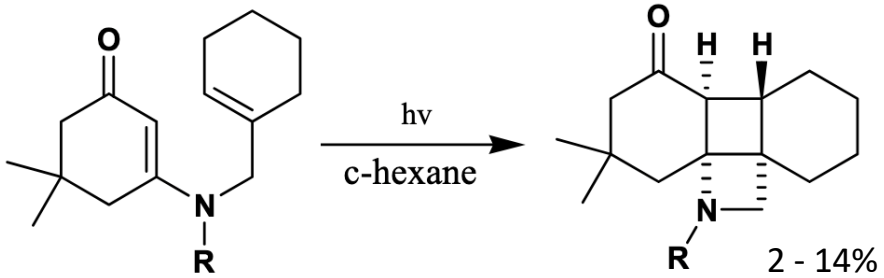


A (R_1, R_2 = Me)



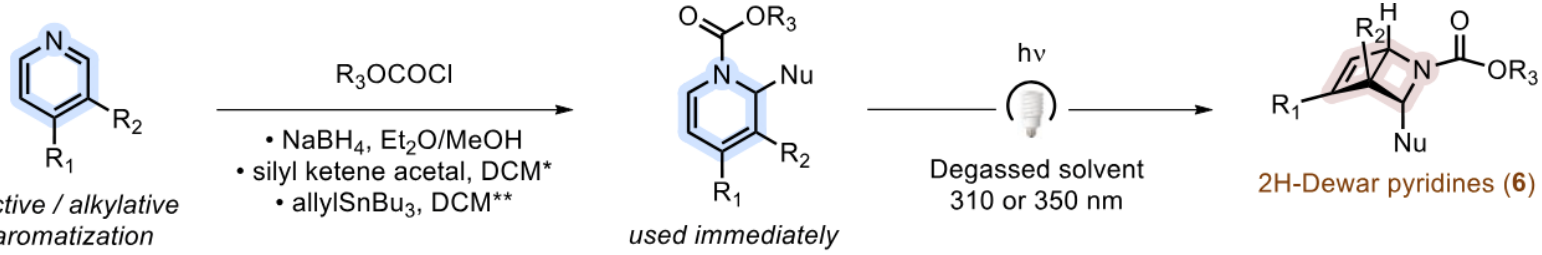
50%

Fowler, *JOC* **1972** *37* 1321



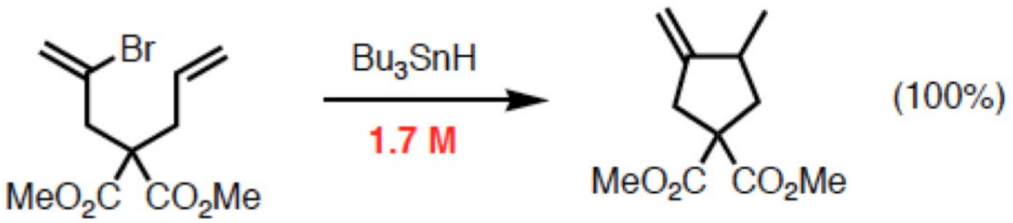
2 - 14%

Swindell *JOC* **1987** *52* 2346

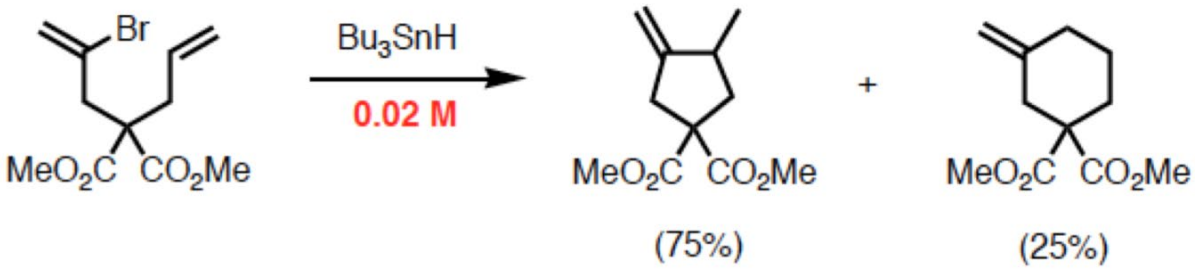


Sarlah *ChemRxiv* **2023** *doi* 10.26434/chemrxiv-2023-jgr4j

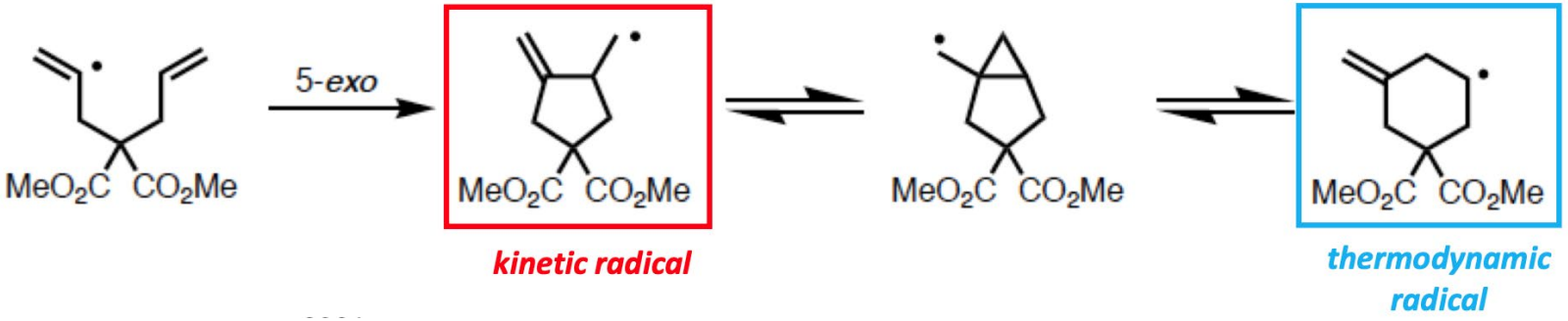
AN OLD LESSON FROM RADICAL CHEMISTRY…



Stork, *JACS* **1982** *104* 2321



Beckwith, Tetrahedron Lett. **1986** *27* 4525



A TRIPLET BIRADICAL VARIANT OF THE STORK-BECKWITH MODEL

ACKNOWLEDGEMENTS

PhD and Post-docs (since 2013): they deserve all credits!

Max Malacria (UPMC)
Etienne Derat (UPMC)
Geraldine Masson (CNRS)
Emmanuel Lacote (Uni Lyon)
Raphael Rodriguez (Curie)
Yanlan Wang (Liaocheng Uni)
Istvan Horvath (CityU HK)
Alexander I. Boldyrev (Utah State)
Alessandro Palmieri (UniCAM)
Stefano Protti (UniPV)

Alessandro Cerveri
Matteo Corrieri
Giulia Russo
Gregoire Boivin
Gabriele Scarica
Matteo Hoch
Sara Sparascio
Maurizio Chiminelli
Davide Ruggeri
Aleksandr Voronov
Nicola Camedda
Andrea Serafino
Chiara Cecchini
Anna Monfredini
Matteo Lanzi
Gianpiero Cera
Davide Balestri
Emanuele Paris
Veronica Santacroce
Tatiana Cañeque-Cobo
Yanlan Wang
Filipe Gomes
Vanessa Narbonne
Pierre-Alexandre Deyris

Andrea Basso, Chiara Lambruschini (UniGE)
Nicolà Della Ca', Raimondo Maggi, Franca Bigi,
Daniele Cauzzi, Luciano Marchiò (UniPR)

Last but not least…

hard cash!

GEA Procomac

otm consulting
Informed decisions for better process.

CORAZZI

ENEA
Agenzia nazionale per le nuove tecnologie, l'energia e lo sviluppo economico sostenibile

AROMA-TRIP
SIR Grant
RBSI14NKFL

Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale
2018-2022

COMP-Hub

COMP-R^3

Dipartimento di Scienze Chimiche, della Vita e della Sostenibilità Ambientale
2023-2027

ART-2-HYDROGEN PNRR GRANT
RSH2A_000009

Finanziato dall'Unione europea
NextGenerationEU

MINISTERO DELL'AMBIENTE
E DELLA TUTELA DEL TERRITORIO E DEL MARE