Ischia Advanced School of Organic Chemistry
Ischia Porto, 27 Set-2 Ott 2008

REARRANGEMENT OF STRAINED ISOXAZOLIDINES: CHEMOSELECTIVE SYNTHESIS OF ASSORTED AZAHETEROCYCLES

Alberto Brandi

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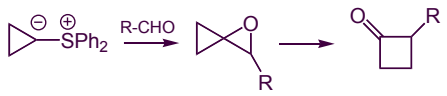
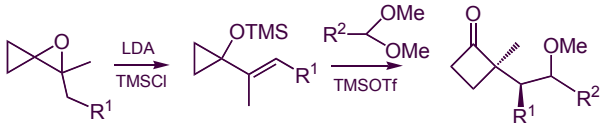
All started .....

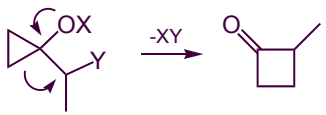


B. M. Trost, M. J. Bogdanowicz *J. Am. Chem. Soc.* **1973**, *95*, 5311
B. M. Trost *Top. Curr. Chem* **1986**, *133*, 3

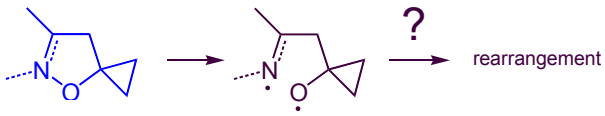


B. M. Trost, A. Brandi *J. Am. Chem. Soc.* **1984**, *106*, 5041

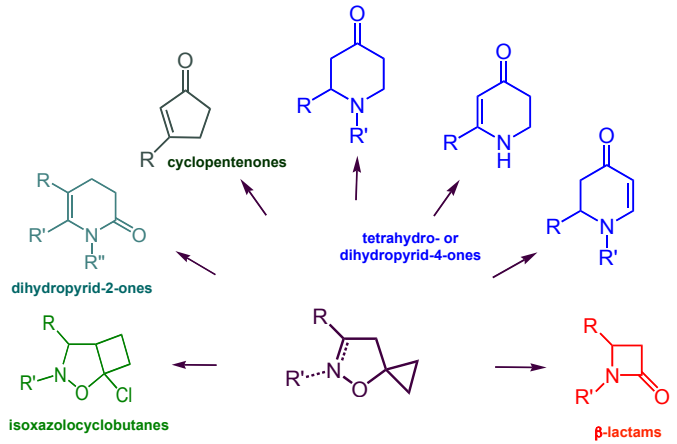
Tiffeneau-Demjanov type rearrangements of cyclopropanol system



working hypothesis: spirocyclopropaneisoxazoline



Chameleon reactivity of spirocyclopropaneisoxazolines

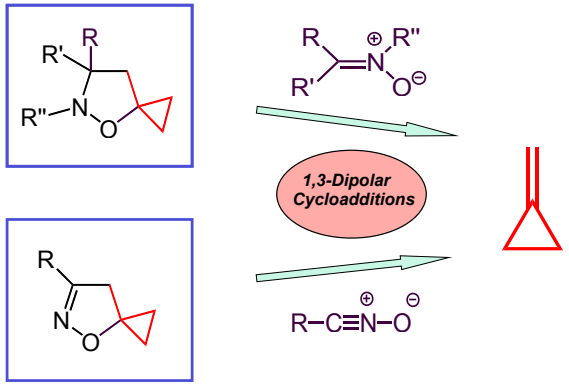


A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem Rev* **2003**, *103*, 1213-1269
A. Brandi, S. Cicchi, F. M. Cordero, *Chem Rev* **2008**, *108*, in press

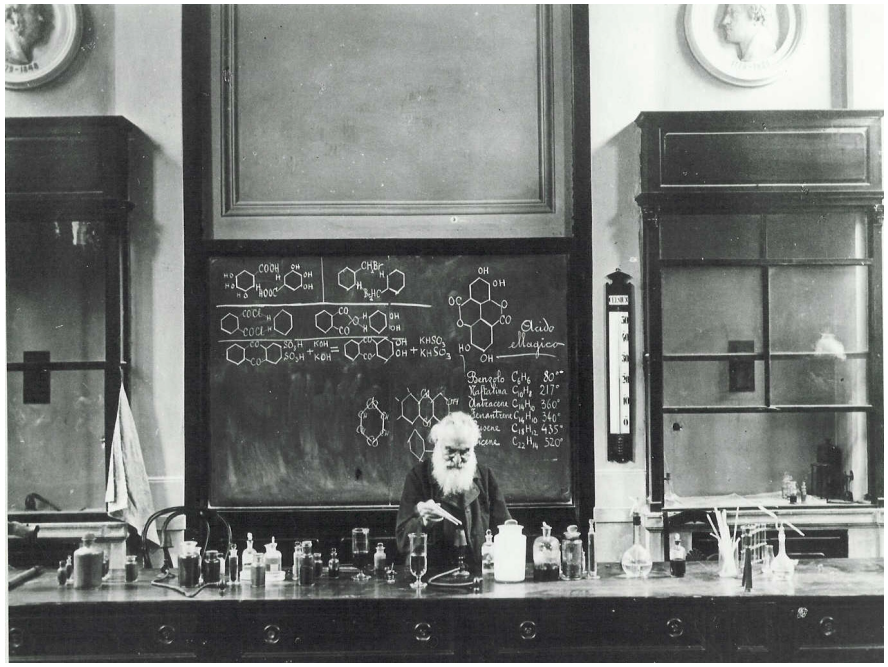
rearrangement of strained isoxazolidines: chemoselective synthesis of assorted azaheterocycles

- Synthesis of spirocyclopropaneisoxazolidines
- Synthesis and reactivity of tetrahydropyrid-4-ones
- Synthesis of 2,3-dihydropyrid-4-ones
- Synthesis and reactivity of b-lactams and b-amino acids

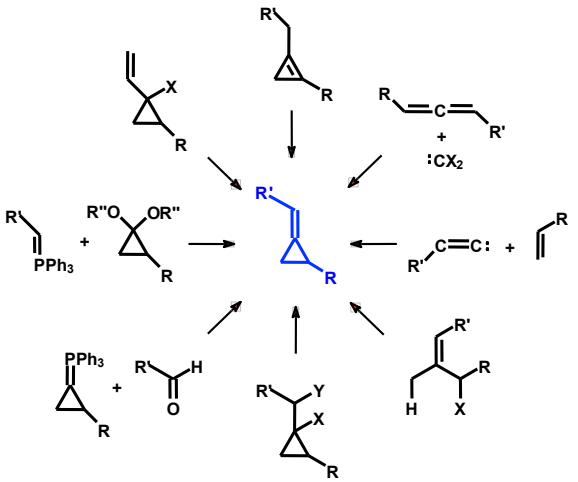
1,3-dipolar cycloadditions to methylenecyclopropane



Synlett **1993**, 1
Top. Curr. Chem. **1996**, *178*, 1-97

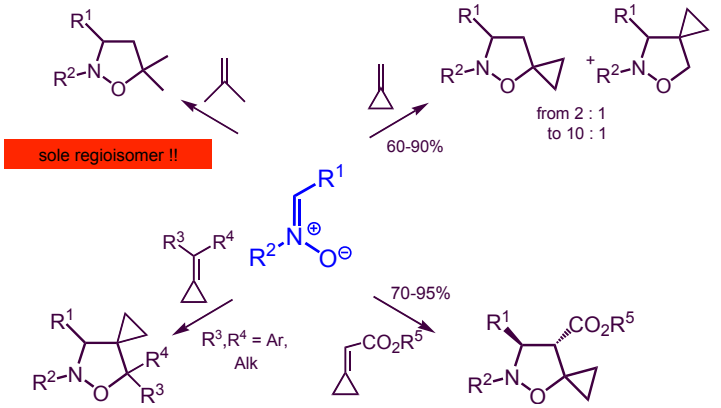


Syntheses of methylene- and alkylidenecyclopropanes



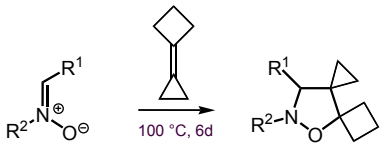
A. Brandi, A. Goti, *Chem. Rev.* **1998**, *98*, 589

Regioselectivity of the cycloaddition

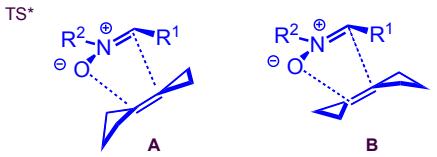


Top. Curr. Chem. **1996**, *178*, 1-97

regioselectivity of cyclobutylidenecyclopropane



R^1	R^2	yield%
Ph	Me	47
Py	Me	85
		48



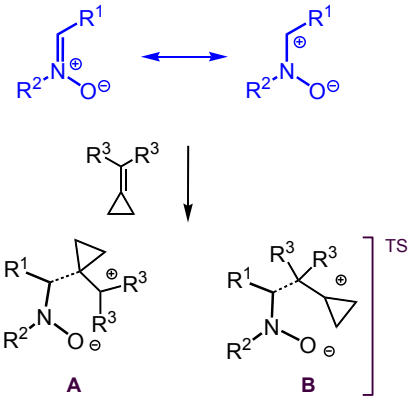
FMO interactions don't justify the regioselectivity

TS* A more stable of **B**: DE_a= 1.8 Kcal/mole (STO 3G level calculations)

calculated $k_A/k_B \approx 11$ at 100 °C

A. de Meijere, A. Brandi et al. *Eur. J. Org. Chem.* **2001**, 3789

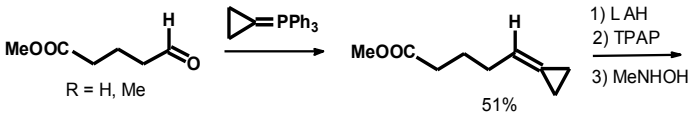
cyclopropane effect: electrophilic attack of the nitrone on alkylidenecyclopropanes?

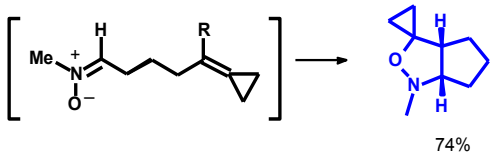


highly polarized Transition States

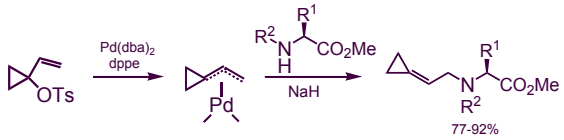
A preferred for stabilization of the positive charge

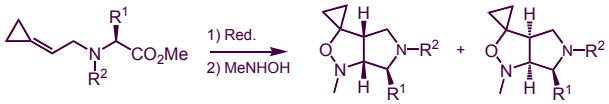
intramolecular cycloadditions





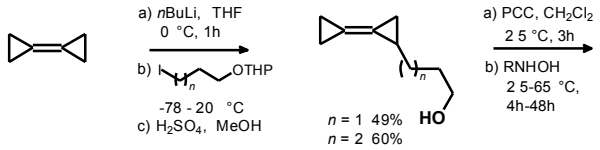
intramolecular cycloadditions

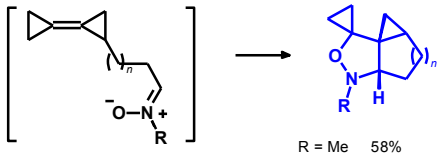




R^1	R^2	Yield %	A:B
H	Ts	71	-
Me	Ts	81	45:55
iPr	Ts	62	39:61
Bn	Ts	74	38:62
Ph	Ts	46	>99:1 (rac)
CH_2Ind	Ts	63	61:39
-$CH_2CH_2CH_2$-		95	>99:1

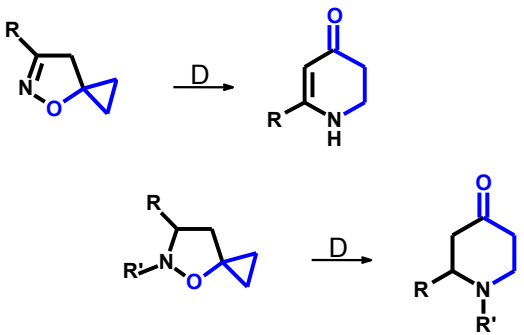
intramolecular cycloadditions





R = Me 58%
Bn 52%
t-Bu 42%

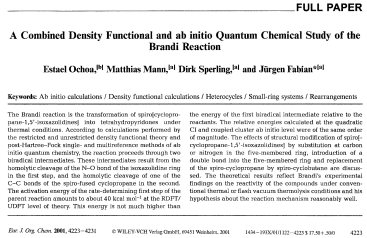
first rearrangement observed (Brandi-Guarna Rearrangement)



- By refluxing in an appropriate solvent between 80-180 °C, or by heating at the same temperatures in a closed vial in an oven.
- Flash Vacuum Thermolysis (FVT) at 400-600 °C.
- Isoxazolines require generally higher temperatures than isoxazolidines

COMPUTATIONAL STUDIES

Prof. Jürgen Fabian
Technische Universitat Dresden, Germany



FULL PAPER

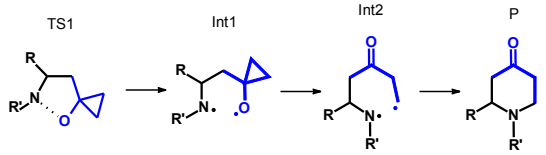
A Combined Density Functional and ab initio Quantum Chemical Study of the Brandi Reaction

Estael Ochoa,[b] Matthias Mann,[b] Dirk Sperling,[b] and Jürgen Fabian*[b]

Keywords: Ab initio calculations / Density functional calculations / Heterocycles / Small-ring systems / Rearrangements

The Brandi reaction is the transformation of spirocyclopropane-1,3′-isoxazolidines[a] into tetrahydropyridones under thermal conditions. According to calculations performed by the restricted and unrestricted density functional theory and post-Hartree–Fock single- and multireference methods of ab initio quantum chemistry, the reaction proceeds through two biradical intermediates. These intermediates result from the homolytic cleavage of the N–O bond of the isoxazolidine ring in the first step, and the homolytic cleavage of one of the C–C bonds of the spiro-fused cyclopropane in the second. The activation energy of the rate-determining first step of the parent reaction amounts to about 40 kcal mol^{-1} at the B3PW91/UDFT level of theory. This energy is not much higher than the energy of the first biradical intermediate relative to the reactants. The relative energies calculated at the quadratic CI and coupled cluster ab initio level were of the same order of magnitude. The effects of structural modification of spirocyclopropane-1,3′-isoxazolidines[a] by substitution at carbon or nitrogen in the five-membered ring, introduction of a double bond into the five-membered ring and replacement of the spiro-cyclopropane by spiro-cyclobutane are discussed. The theoretical results reflect Brandi's experimental findings on the reactivity of the compounds under conventional thermal or flash vacuum thermolysis conditions and his hypothesis about the reaction mechanism reasonably well.

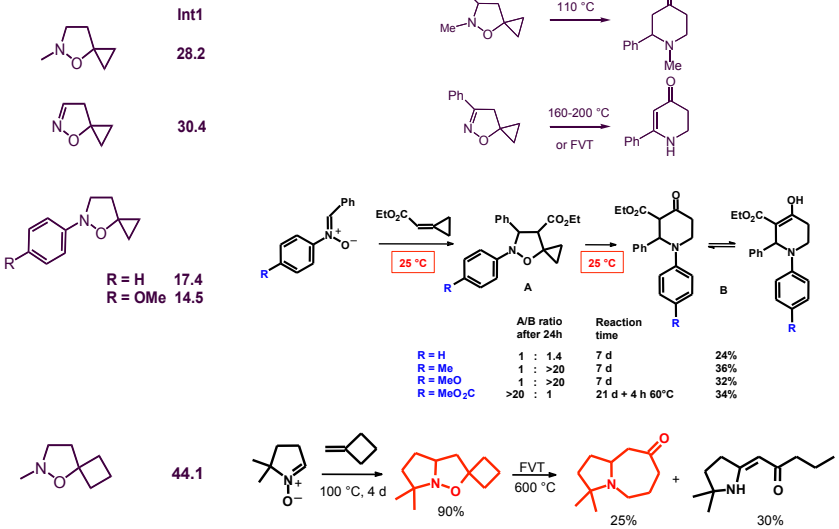
Eur. J. Org. Chem. **2001**, 4223–4231 1434–193X/01/1122–4223 $ 17.50+.50/0



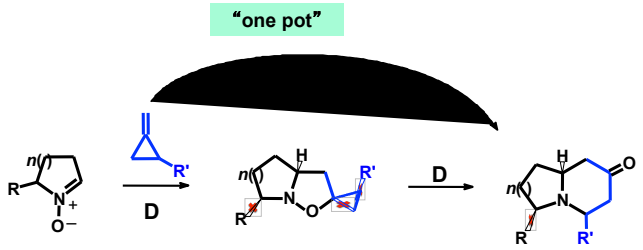
	TS1	Int1	Int2	P
R=R' = H	36.5	31.1	20.4	-58.4
R= Me; R' = H	--	34.8	20.6	-58.7
R= H; R' = Me	32.8	28.2	16.5	-61.8

(U)DFT/B3LYP/6-31G*
Energies in kcal/mol

(U)DFT/B3LYP/6-31G*
Energies in kcal/mol

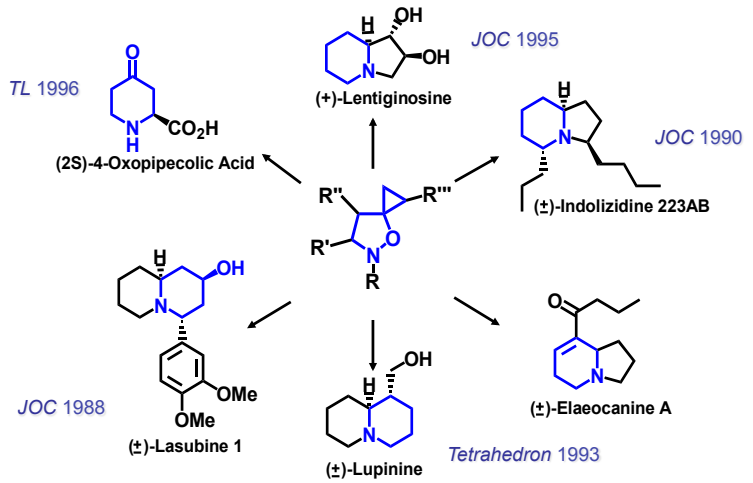


The cyclic nitrone route to aza-bridgehead heterocycles



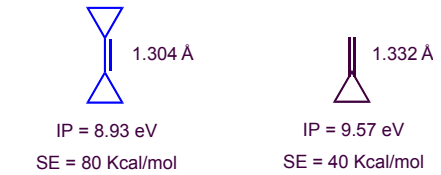
- high atom economy
- complete control of regioselectivity
- high control of stereoselectivity

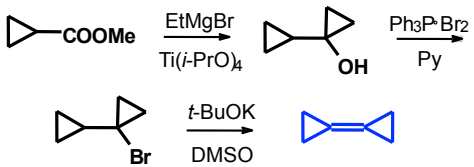
Chem. Rev. **2003**, *103*, 1213-1269



Bicyclopropylidene:
an unique olefin

J. M. Conia et al.
Tetrahedron Lett. **1970**, 1587
Angew. Chem., Int. Ed. Engl. **1973**, *12*, 332





A. de Meijere, S. I. Kozhushkov, T. Spaeth, N. S. Zefirov *J. Org. Chem.* **1993**, *58*, 502

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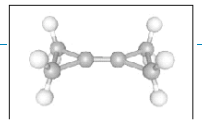
Star Team Designation

Bicyclopropylidene:
an highly energetic material

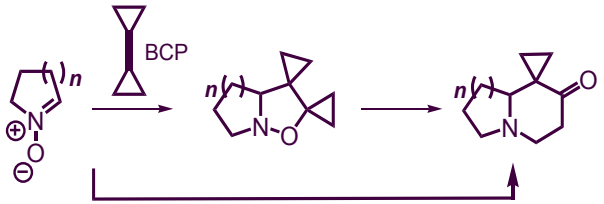
Air Force Office of Scientific Research 2000 'Star Team'

ERC research scientists at the Air Force Research Laboratory Propulsion Directorate at Edwards Air Force Base received the Air Force Office of Scientific Research Star Team designation for research excellence in the areas of Combustion and Plumes, High Energy Density Matter, and Hybrid Polymer Development. This award recognized outstanding basic research accomplishments in support of Air Force technology needs in the rocket propulsion technology area. Research accomplishments included advances in chemical synthesis of new more energetic rocket propellants and propellant ingredients; advances in the development, synthesis, and characterization of new inorganic/organic monomers and polymers; and accomplishments in the understanding of the chemical kinetics of gases found in rocket engines during combustion.

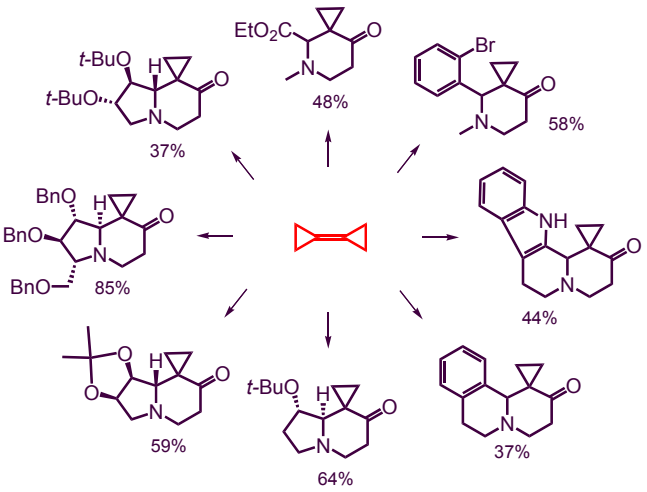


ERC researchers developed a simpler and less expensive method of producing large quantities of the energetic hydrocarbon fuel called Bicyclopropylidene.

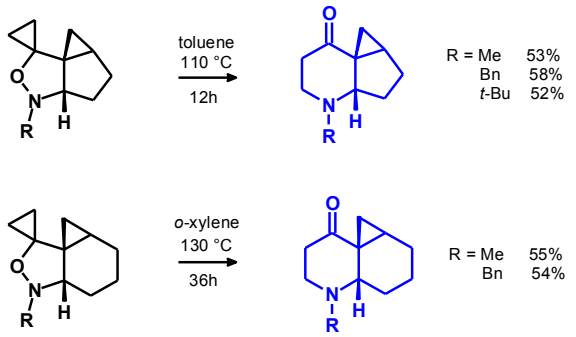
Bicyclopropylidene: an unique olefin



Alberto Brandi – Dept. of Organic Chemistry "U. Schiff", UNIFI

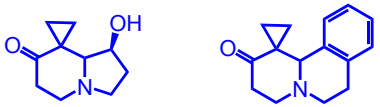


Alberto Brandi – Dept. of Organic Chemistry "U. Schiff", UNIFI

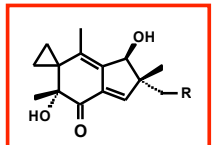


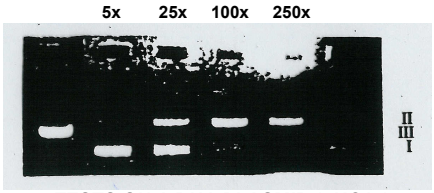
Alberto Brandi – Department of Organic Chemistry "U. Schiff"

putative alkylating activity against DNA: like illudines



aza-illudine analogues



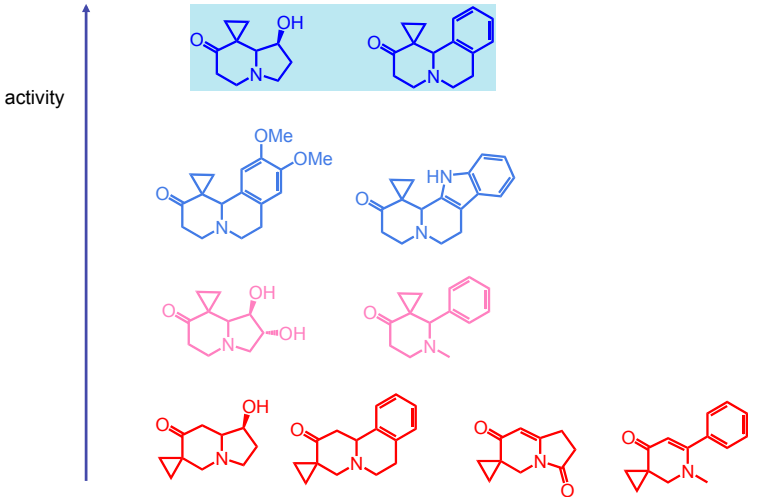


TESTS ON A DNA PLASMID (pUC19)

Brandi, de Meijere et al.
J. Org. Chem. **1996**, *61*, 1665
Synlett **1997**, 25

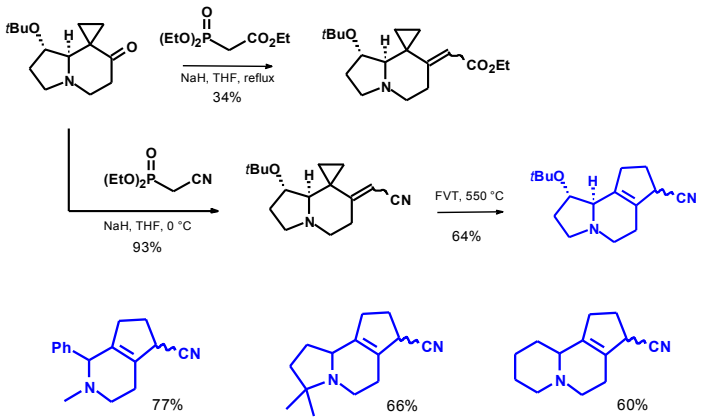
structure/activity investigation

activity



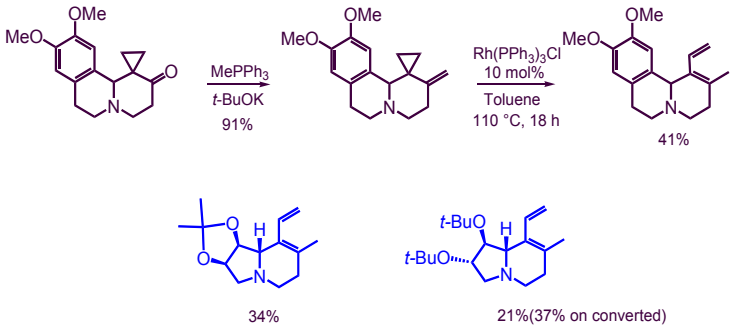
J. Org. Chem. **1999**, *64*, 7846

cyclopentenylation reactions



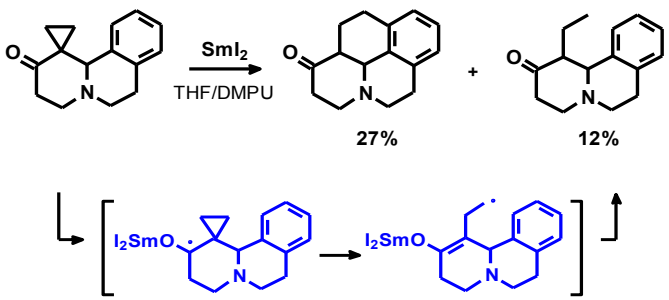
Synlett **2001**, 433

synthesis of dienes



unpublished results

SmI_2 opening of the spirocyclopropane ring

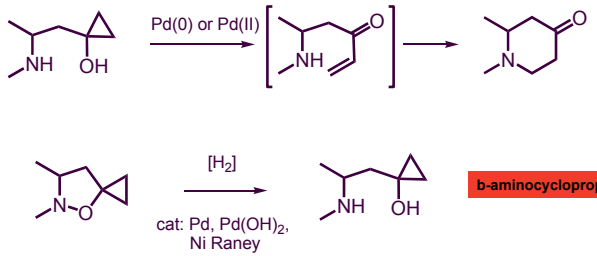


unpublished results

new chemoselective Pd catalysed rearrangement of reduced isoxazolidines

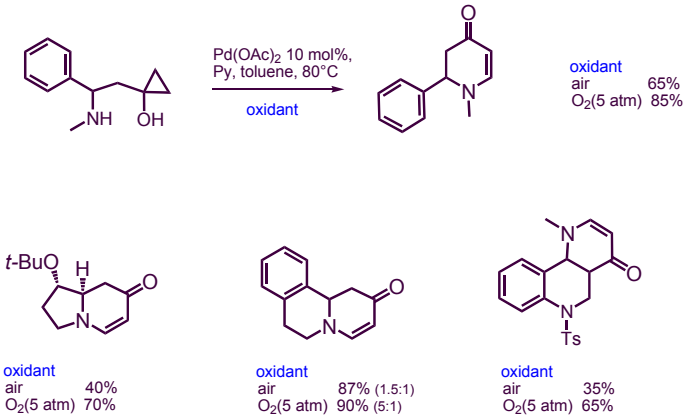
Pd(0): Okumoto, H.; Jinnai, T.; Shimizu, H.; Harada, Y.; Mishima, H.; Suzuki, A. *Synlett* **2000**, 629
Pd(II): Park, S.-B.; Cha, J. K. *Org. Lett.* **2000**, *2*, 147

working hypothesis:

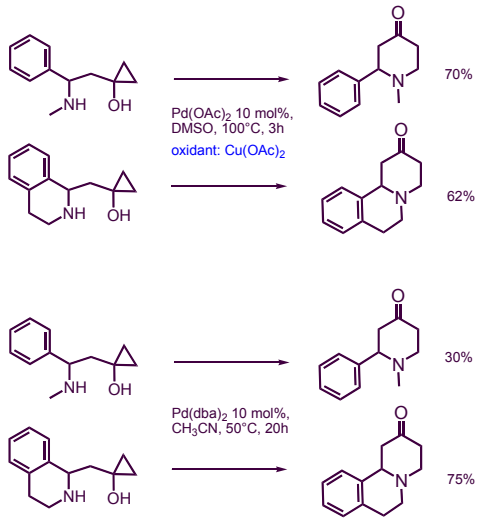


SmI_2 (yield 70-90%) *Tetrahedron Lett.* **2004**, *45*, 8375

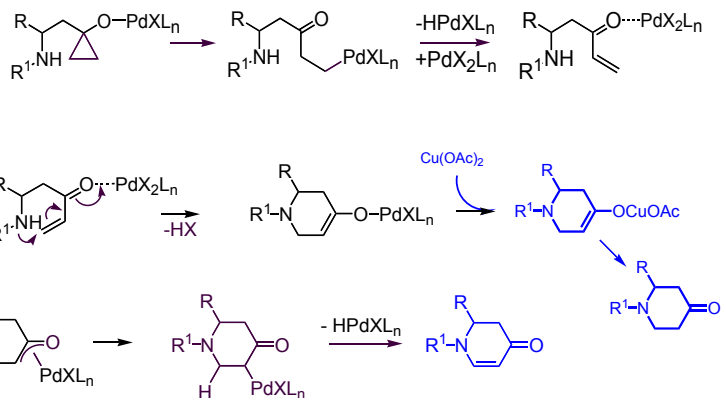
2,3-dihydropyrid-4-ones



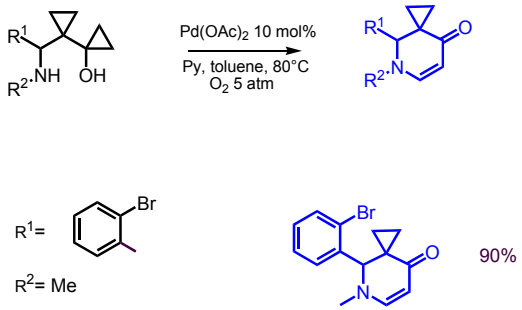
J. Org. Chem. **2005**, *70*, 5636



proposed mechanism for formation of 2,3-dihydropyrid-4-ones

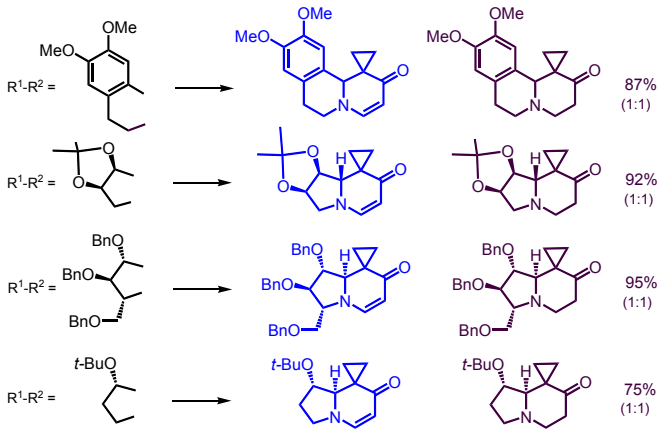


a-cyclopropane-b-aminocyclopropanols

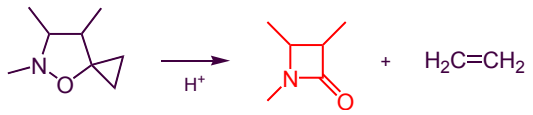


Eur. J. Org. Chem., **2008**, 1085

spirocyclopropane pyridin-4-ones

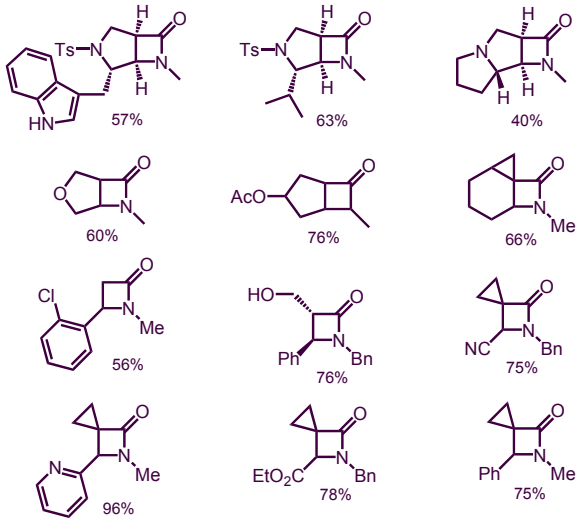


domino rearrangement/fragmentation process: new general synthesis of b-lactams

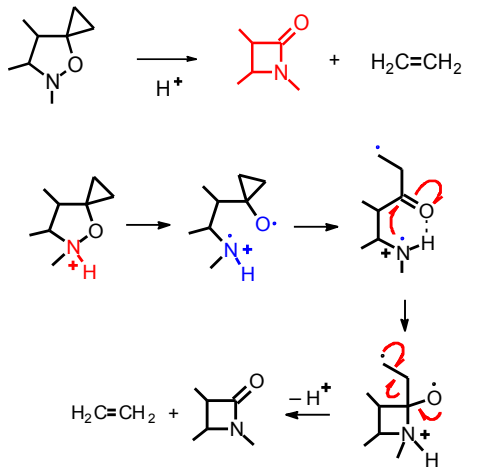


F. M. Cordero, F. Pisaneschi, A. Goti, J. Ollivier, J. Salaün, A. Brandi, *J. Am. Chem. Soc.* **2000**, *122*, 8075
F. M. Cordero, F. Pisaneschi, M. Salvati, V. Paschetta, J. Ollivier, J. Salaün, A. Brandi *J. Org. Chem.* **2003**, *68*, 3271

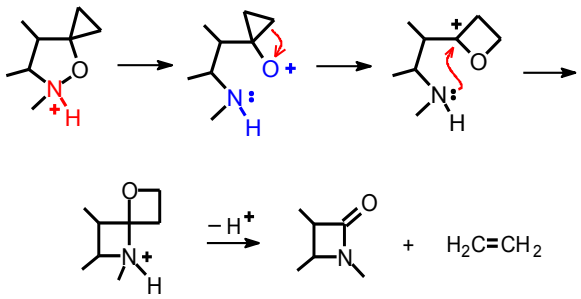
reaction conditions:
- **Protic acid:** HCl, TFA or *p*-TsOH, 1 ÷ 1.2 eq.
- **Solvent:** toluene, EtOH or CH_3CN
- **Temperature:** 70 °C ÷ 110 °C
- **Reaction time:** 30 min ÷ 1 h



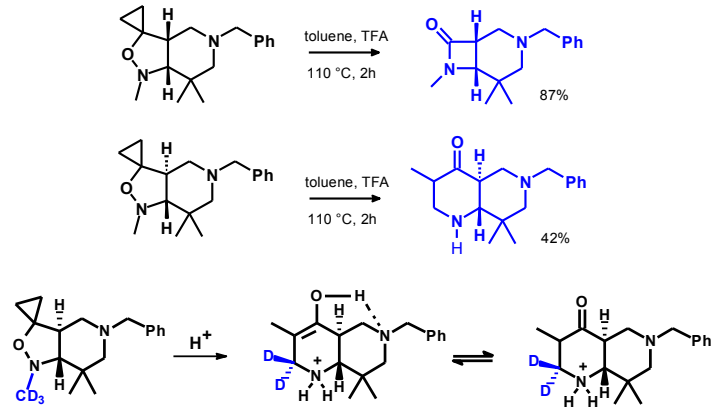
proposed mechanism for formation of b-lactams



another possible mechanism for formation of b-lactams



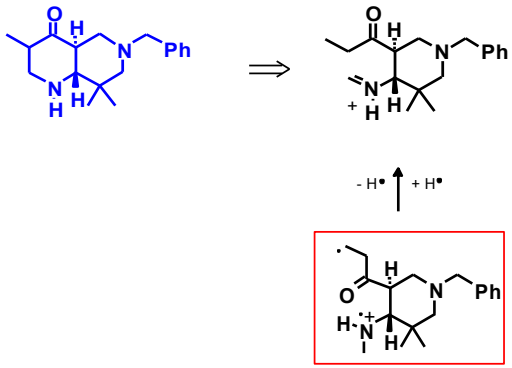
support to the proposed mechanism



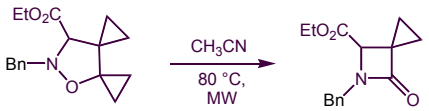
deuteromethylene insertion in the tetrahydropyridone ring

J. Org. Chem. **2003**, *68*, 3271

support to the proposed diradical mechanism



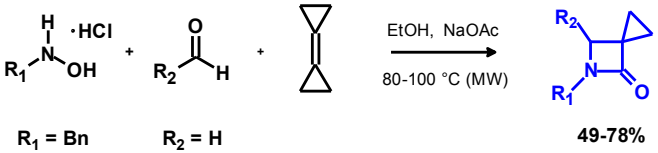
other acid and Lewis acid induced rearrangement



LA (2 equiv)	time min	yield%
$NH_2OH.HCl$	25	43
$BF_3.Et_2O$	15	67
TMSCl	10	80
$MgCl_2$	20	41
$TiCl_4$	5	67
$Sc(OTf)_3$	10	61

unpublished results

three component synthesis of spirocyclopropane-b-lactams



R_1 = Bn, = PMB, = Ph_2CH, = *t*Bu, = Me

R_2 = H, = CO_2Me, = CO_2Et

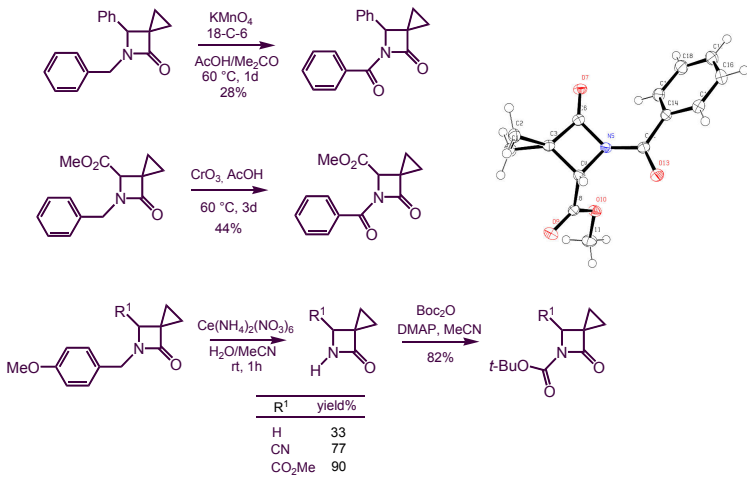
49-78%

A. Zanobini, A. Brandi, A. de Meijere, *Eur. J. Org. Chem.* **2006**, 1251

R^1	yield%
Bn	68
PMB	53
BnH	49
t-Bu	73

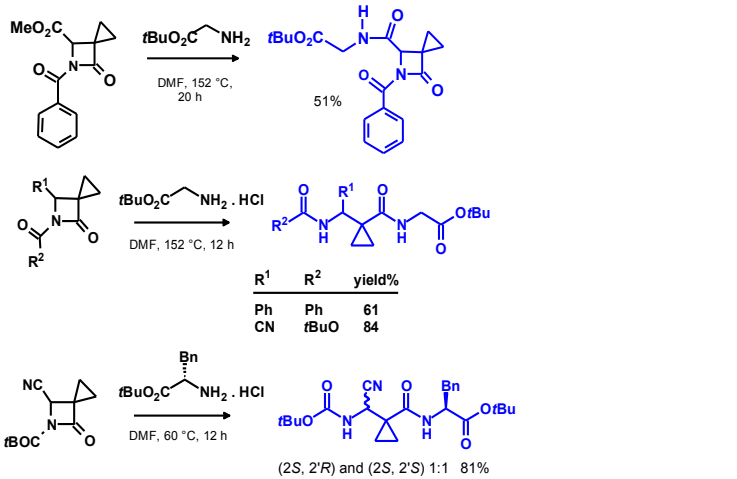
R^1	R^2	yield%
Bn	Et	72
t-Bu	Et	53
PMB	Me	78

changing the character of the *N*-protecting group



R^1	yield%
H	33
CN	77
CO_2Me	90

synthesis of dipeptides

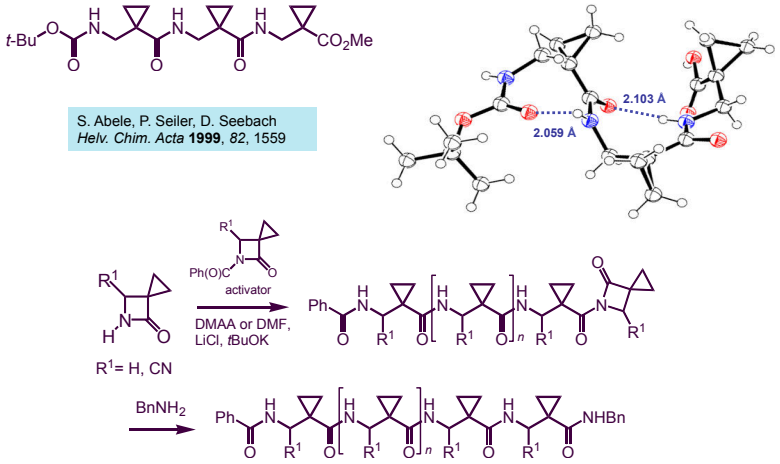


R^1	R^2	yield%
Ph	Ph	61
CN	*t*BuO	84

(2*S*, 2'*R*) and (2*S*, 2'*S*) 1:1 81%

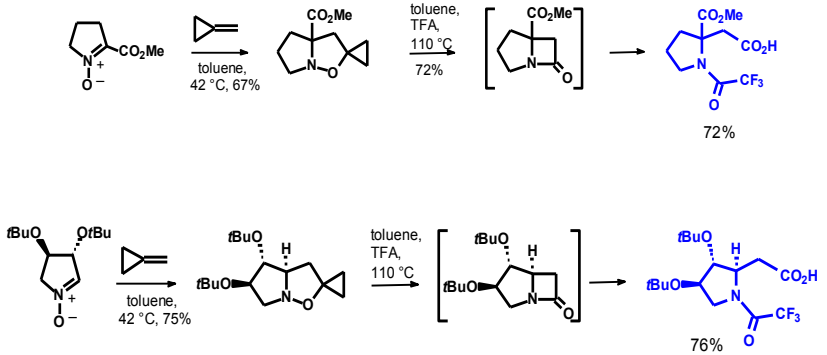
Eur. J. Org. Chem. **2004**, 4158

poly(b-peptide): poly-1-aminomethyl-cyclopropanecarboxylic acid



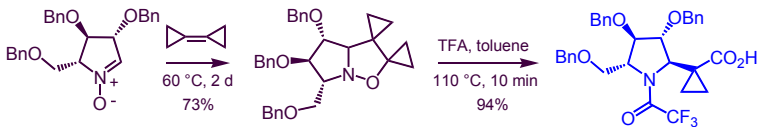
A. Zanobini, 2005, PhD thesis, Göttingen, Germany

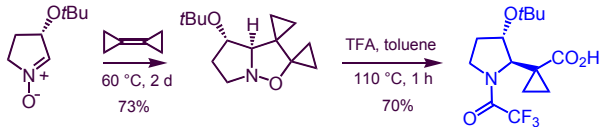
b-proline type compounds



Eur. J. Org. Chem. **2004**, 2205

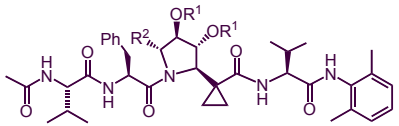
cyclopropanated b-proline type compounds



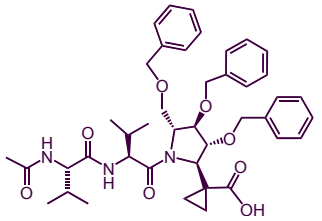


unpublished results

antiviral synthetic targets

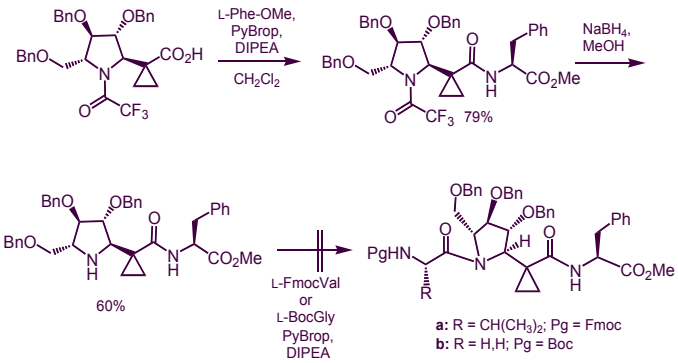


Inhibitors of HIV aspartic proteases
F. Benedetti, et al.
Bioorg. Med. Chem. ***2003****, 11, 4719*

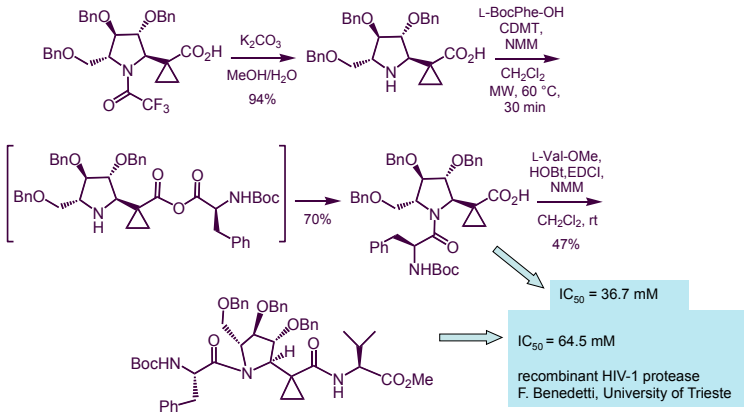


Inhibitors of HCV serine proteases
J. Rancourt, et al.
J. Med. Chem. ***2004****, 47, 2511*
J. Med. Chem. ***2004****, 47, 6584*

synthesis of tripeptide Val-Xxx-Phe



synthesis of tripeptide Phe-Xxx-Val



unpublished results

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