

**ОБРАЩЕНИЕ ТРАДИЦИОННОЙ РЕАКЦИОННОЙ СПОСОБНОСТИ
КАРБОНИЛЬНОЙ ГРУППЫ И АЛИФАТИЧЕСКИХ НИТРОСОЕДИНЕНИЙ.**

С.Л. ИОФФЕ

*Институт органической химии им. Н.Д.Зелинского Российской Академии Наук,
E-mail: iof@ioc.ac.ru*

(Презентация сообщения. Красновидово, 20 января 2015 года.)



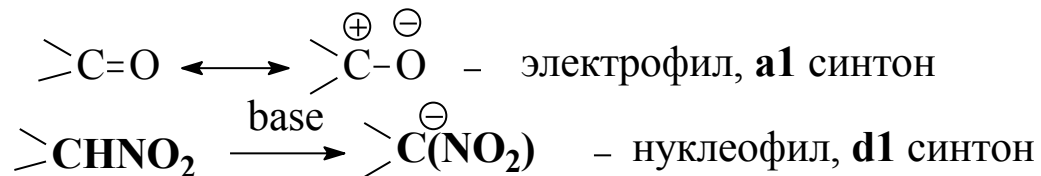
Обращение реакционной способности (reactivity umpolung) — изменение реакционной способности той или иной функциональной группы на противоположную

D. Seebach, "Methods of Reactivity Umpolung", *Ang. Chem. Int.Ed.*, **18**(4), 239-258 (1979)

PROF. DIETER SEEBACH (SWITZERLAND)

Dieter Seebach was born in Karlsruhe in 1937 and studied chemistry at the local Technische Hochschule (now KIT), where he received a PhD degree in 1964 with a thesis on small-ring compounds and peroxides (supervisor: R. Criegee). After a two-year stay at Harvard University as a Postdoctoral Fellow (with E. J. Corey) and Lecturer he returned to Karlsruhe for a Habilitation (1969) on S- and Se-stabilized carbanion and carbene derivatives. In 1971 he became Full Professor at the Justus-Liebig University Giessen and in 1977 he moved to ETH Zurich. He held longer-term guest professorships at the University of Wisconsin (Madison), Caltech (Pasadena), and Harvard University. Since 2003 Seebach has been Professor Emeritus at ETH, where he leads a group of postdoctoral co-workers in research mainly on b-peptides and the mechanism of organocatalysis.

Рассмотрим взаимоотношения между карбонильной группой и фрагментом >CH(NO₂).



Методологически возможны два подхода к осуществлению umpolung:

- 1) обратимая замена функциональной группы $>C=O \rightleftharpoons >CHNO_2$;
- 2) изменение реакционной способности (reactivity umpolung) функциональной группы.

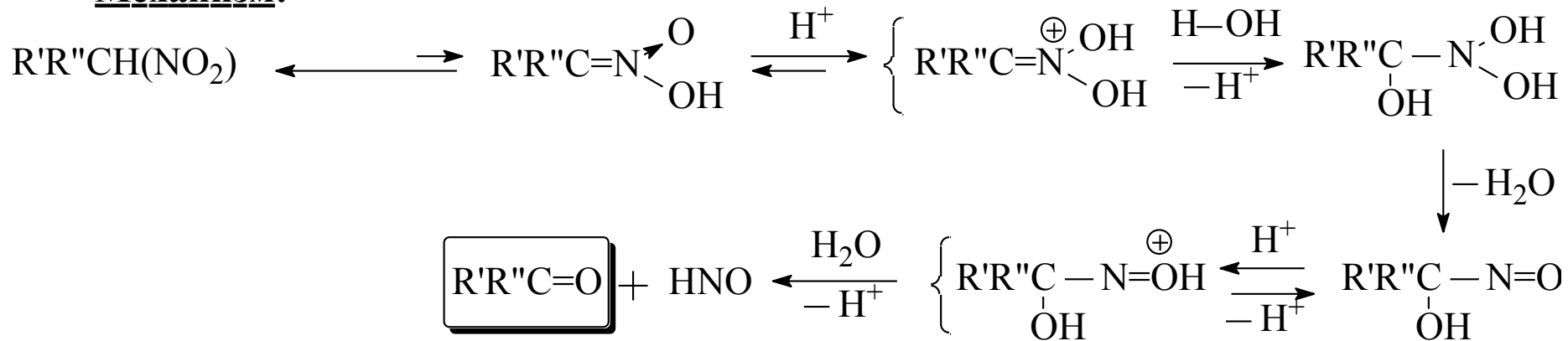
Переход от нитросоединений к карбонильным соединениям.

Реакция Нефа.

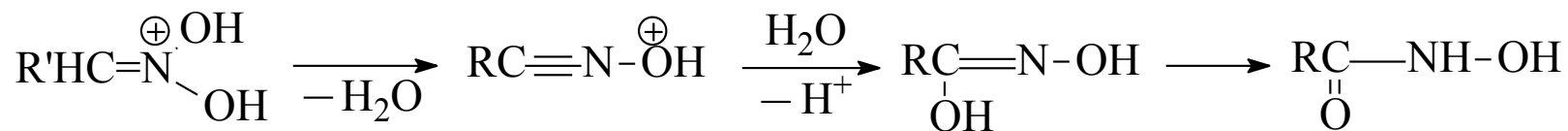


Универсальный способ трансформации алифатических нитросоединений в карбонилсодержащие субстраты.

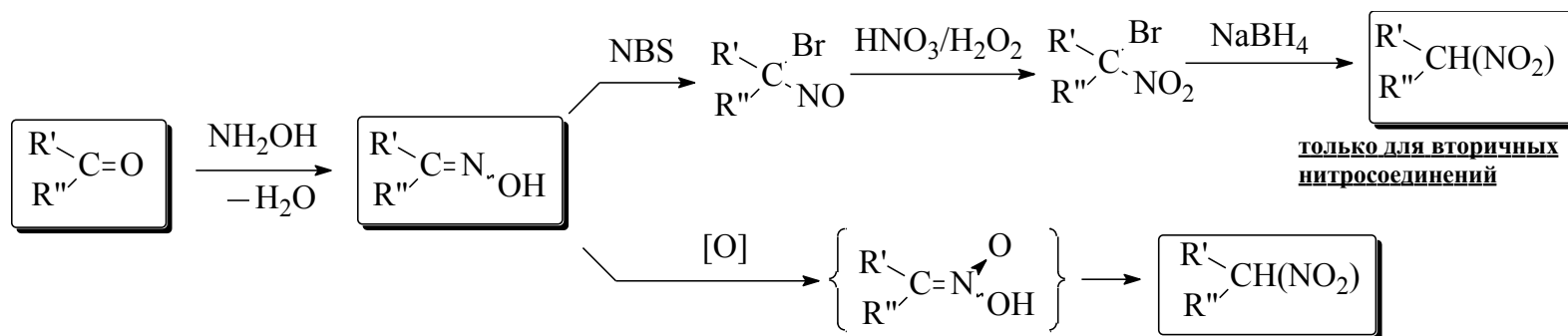
Механизм:



Если $R''=H$, возможен также переход через протонированные окиси нитрилов

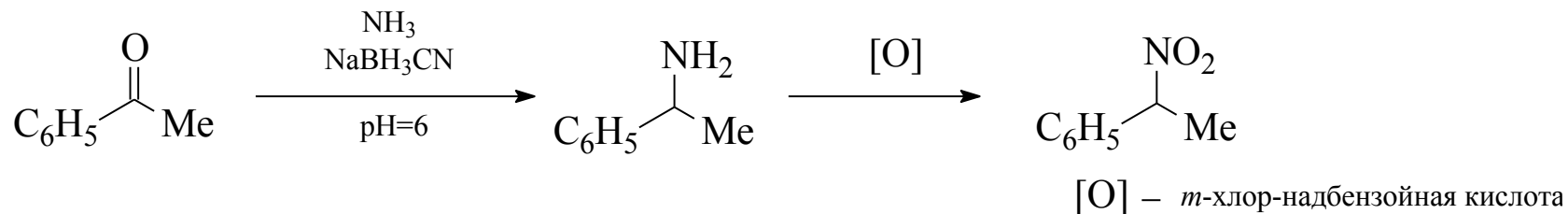


Пути превращения карбонилсодержащих субстратов в алифатические нитросоединения.



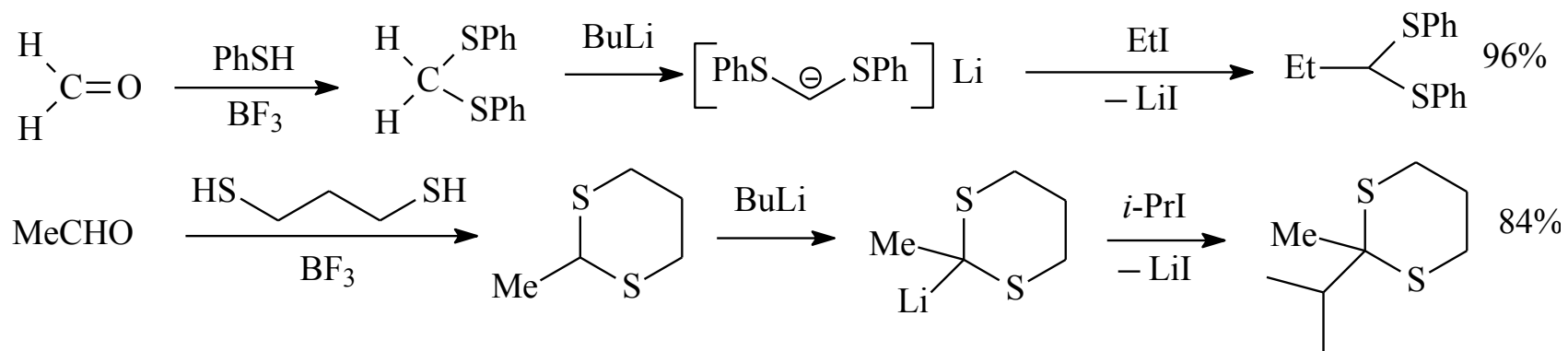
только для вторичных нитросоединений

[O] – CF_3CO_3H , $K_2Cr_2O_7/MeCO_2H$ и т.п.

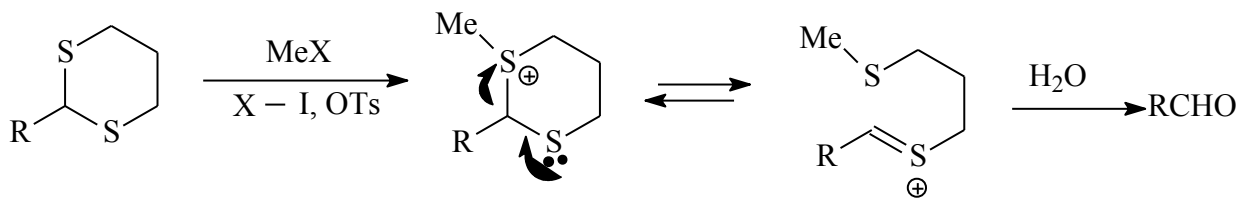
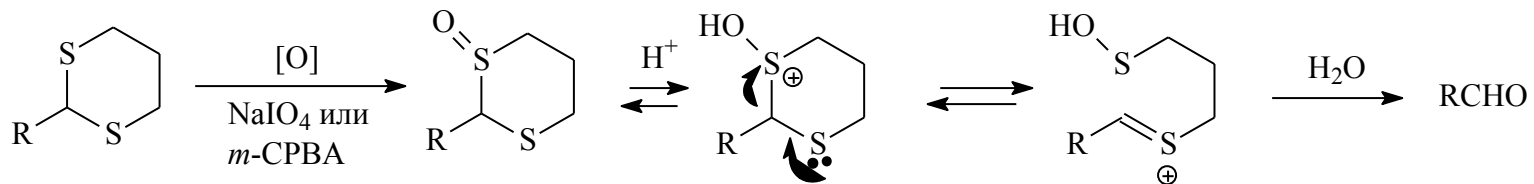
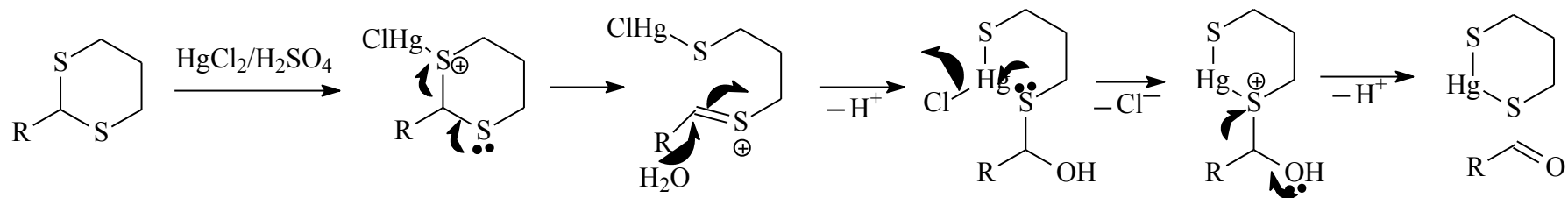


Имеются методологические проблемы с трансформацией альдегидов в первичные нитросоединения.

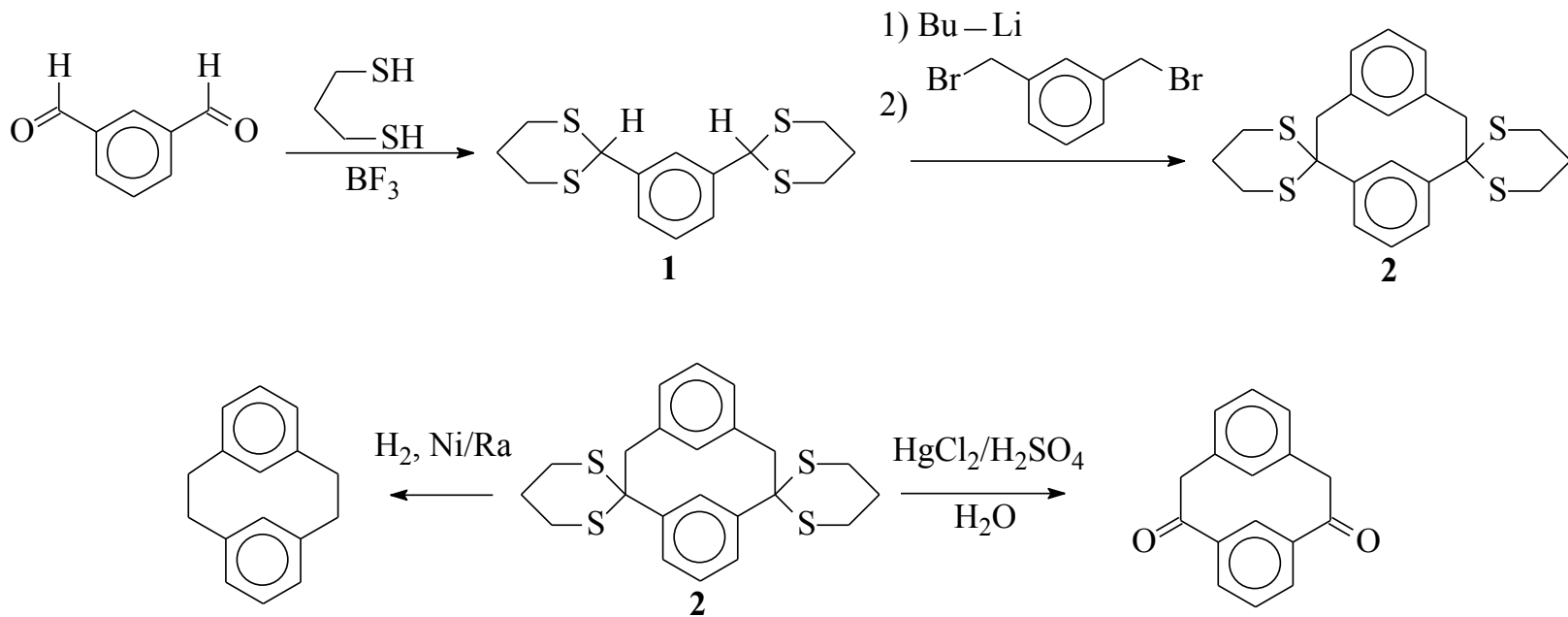
Обращение реакционной способности карбонильной группы.



Пути трансформации дитианов в карбонильные соединения.

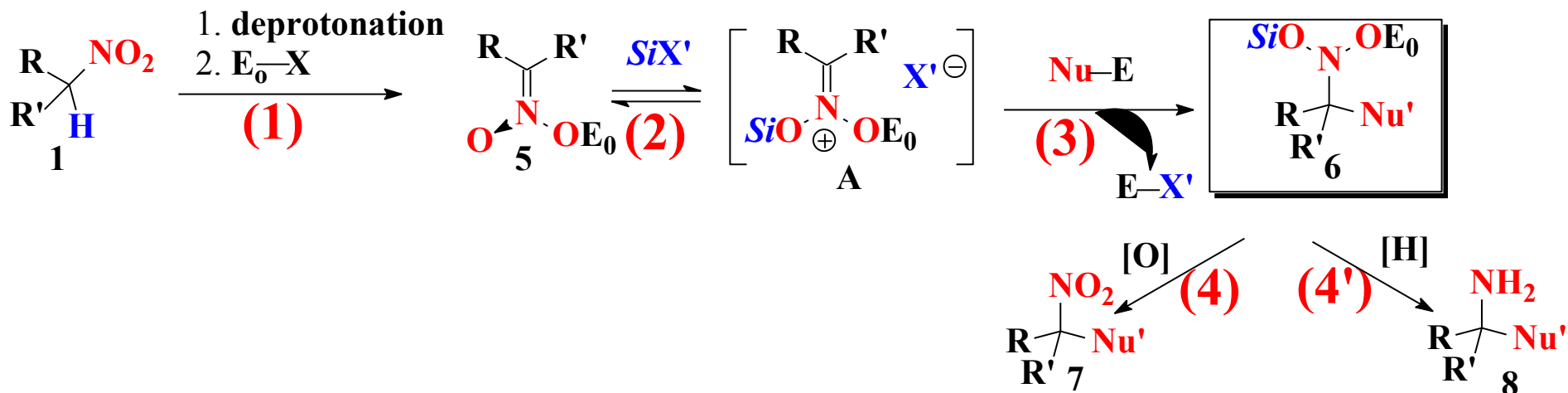


Синтезы циклофанов.



New approach to Umpholung of Reactivity of aliphatic nitro compounds.

(*Eur.J.Org.Chem.*, 2012, 3377)



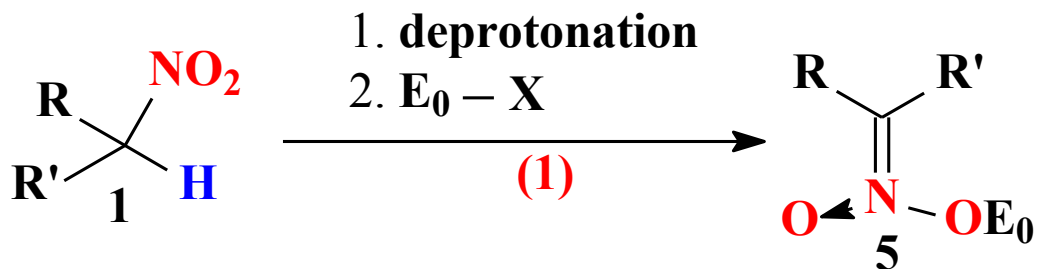
E_0X - alkylating or silylating agent;

SiX' - silyl Lewis Acid;

$Nu-E$ - π -nucleophile; E -electrofug;

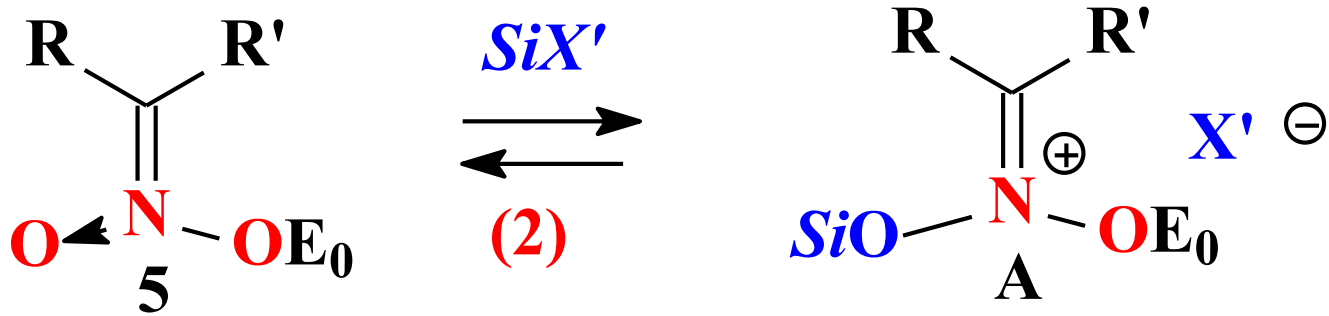
Nu' -a fragment of nucleophile with π -system transformed.

Реализация первой стадии:



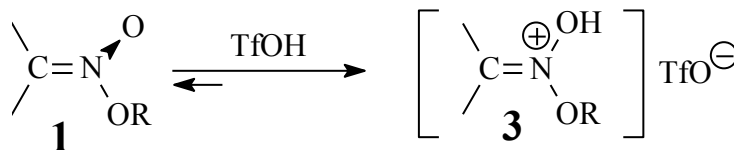
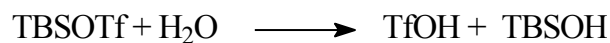
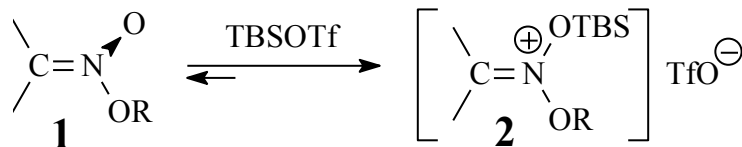
S.L.Ioffe in book "Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis.", 2008, second ed., Ed. by H. Feuer, A John Wiley & Sons, Inc., Hoboken, New Jersey, pp. 435 – 748

Реализация второй стадии:



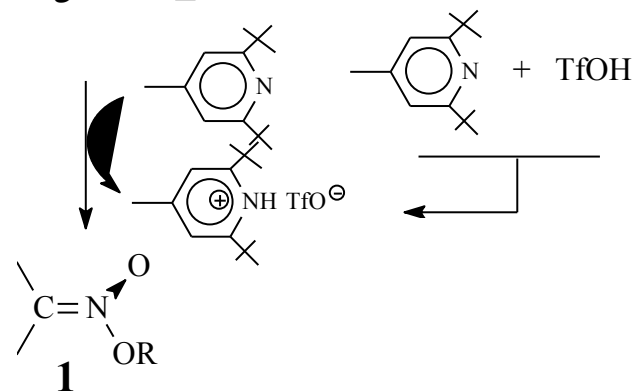
The especial procedure for direct observations of N,N-bis-oxy-iminium cations.

(with minimization of side processes).



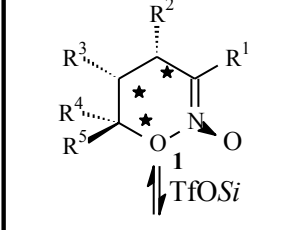

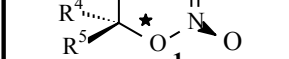
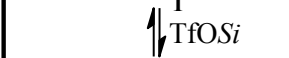
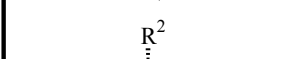
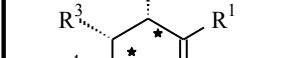
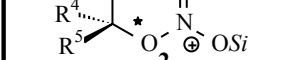
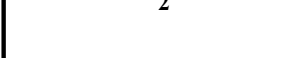
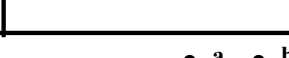

TBS — SiMe₂Bu^t

. the cations of long life



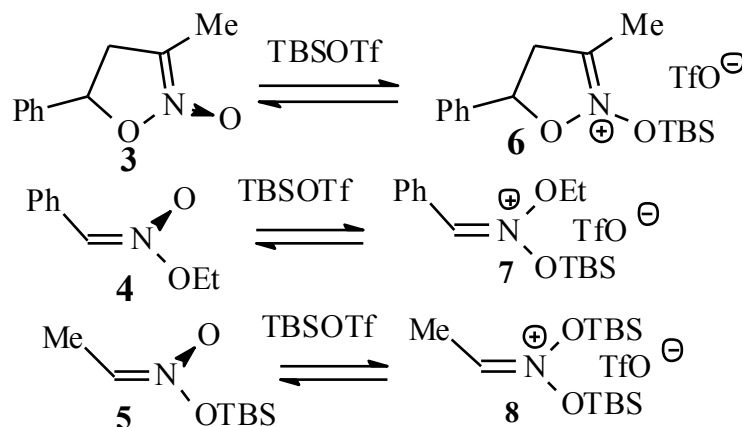
NMR observations of N,N-bis-oxy-iminium cations.

Yu.A. Khomutova, V.O. Smirnov, H. Mayr,
S.L. Ioffe, *J. Org. Chem.*, 2007, 73, 9134.

	Катион	Si	R ¹	R ²	R ³	R ⁴	R ⁵
	2a	TBS	H	Ph _{eq}	H	Me	Me
	2a'	TMS	H	Ph _{eq}	H	Me	Me
	2b	TBS	Me	Ph _{eq}	H	Me	Me
	2c^a	TBS	H	An _{eq}	H	H	OEt _{eq}
	2c^b	TBS	H	An _{ax}	H	H	OEt _{ax}
	2d	TBS	H	Ph _{eq}	H	Ph	H
	2e	TBS	H	Ph _{eq}	H	Me	OMe _{ax}
	2f	TBS	H	OCOAr _{ax}	H	Me	Me
	2g'	TMS	H	An _{eq}	-(CH ₂) ₆ -		OMe _{ax}

$2c^a : 2c^b = 1.5 : 2$

TBS - SiMe₂Bu^t; TMS - SiMe₃



Charakteristic paramethers:

α -¹³C (C-3) – 20 – 40 ppm in low field

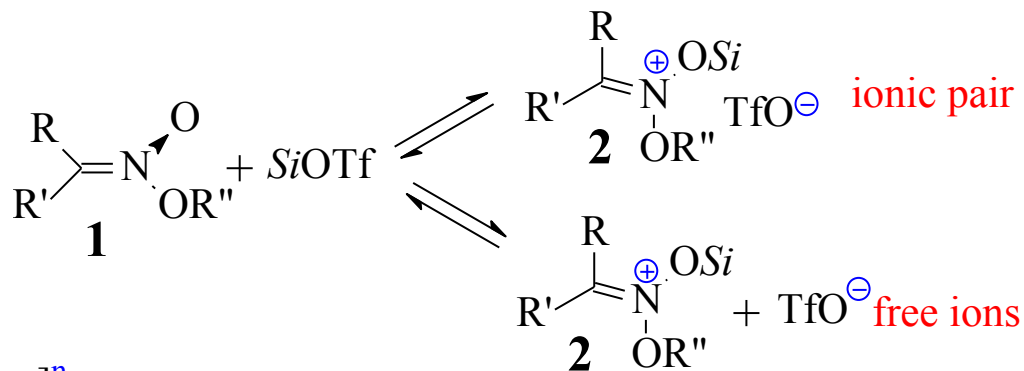
β -¹³C (C-4) – 5 – 10 ppm in low field

γ -¹³C(C-5) – 5 – 10 ppm in low field

H -C_α – 1.5 – 2.0 ppm in low field

δ ²⁹Si ≈ 50 ppm

Bis-oxy-iminium cations in CD₂Cl₂.



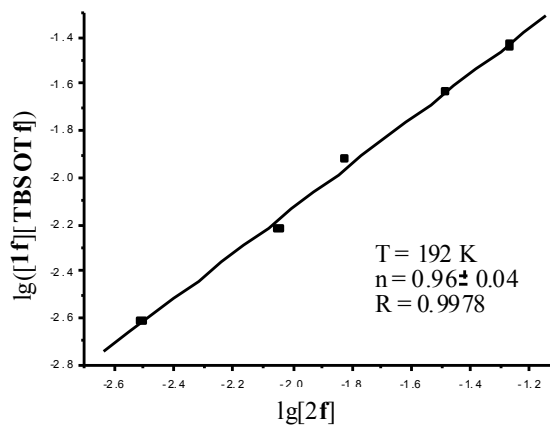
$$K = \frac{[\text{cation}]^n}{[\text{nitronate}][\text{TfOSi}]}$$

$$\lg K = n \lg[\text{cation}] - \lg[\text{nitronate}][\text{TfOSi}]$$

$$\lg[\text{nitronate}][\text{TfOSi}] = n \lg[\text{cation}] - \lg K$$

n=1, ionic pair

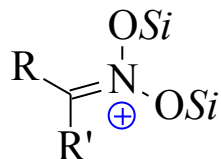
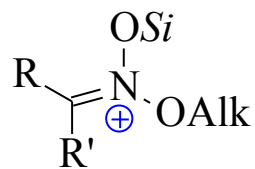
n=2, free ions



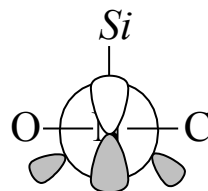
The salts **2** exist as ionic pairs. Decrease of reagents concentration moves an equilibrium aside of initial nitronates **1**.

Stereodynamic processes in N,N-bis-oxy-iminium cations.

Acyclic iminium cations

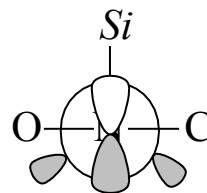
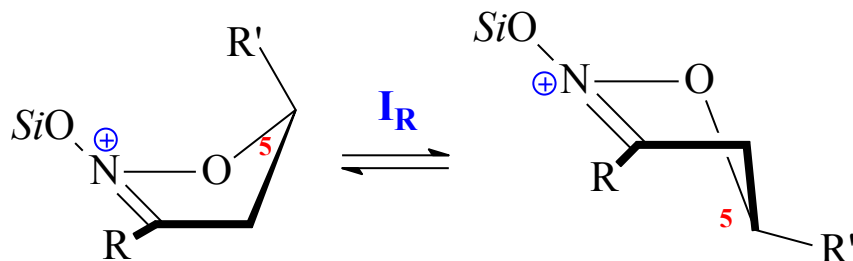


configuration is stable (??)



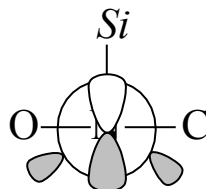
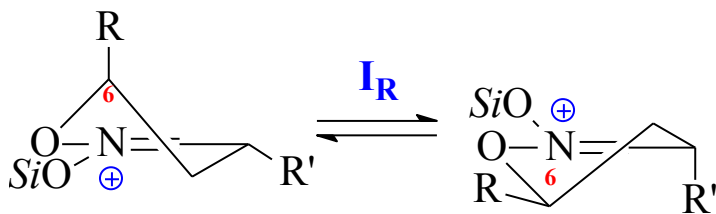
Slow rotation around N—OSi bond.

Five-membered cyclic iminium cations.



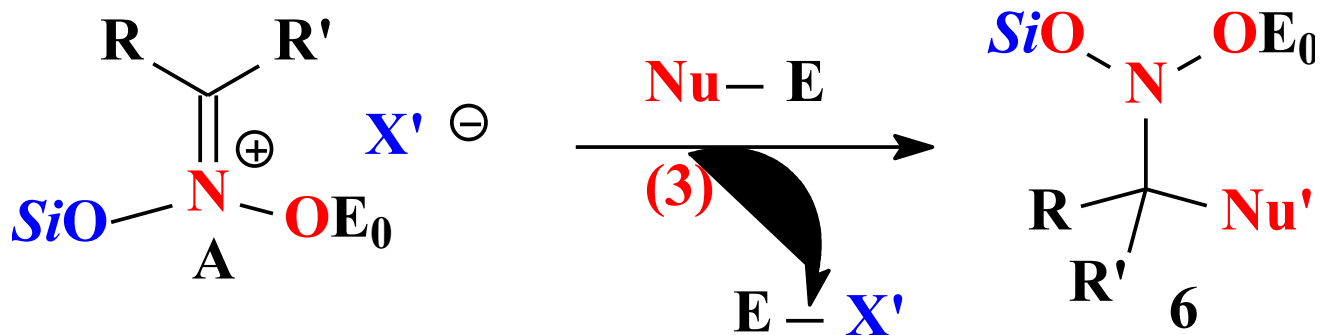
Slow rotation around exocyclic N—OSi bond.

Six-membered cyclic iminium cations.

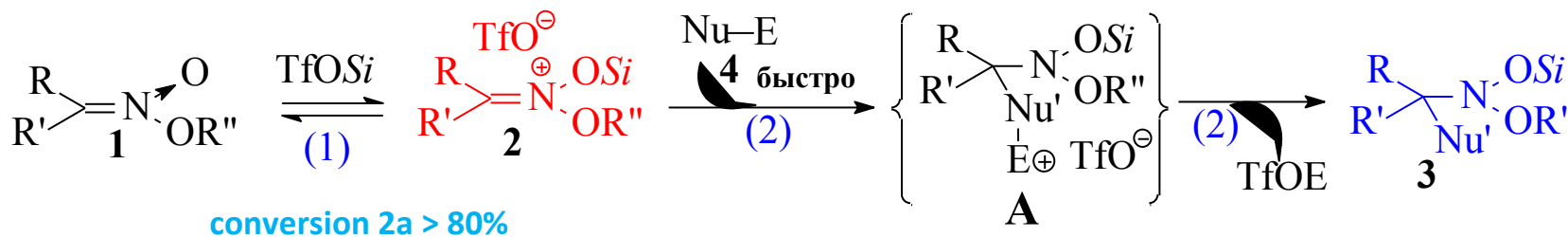


Slow rotation around exocyclic N—OSi bond.

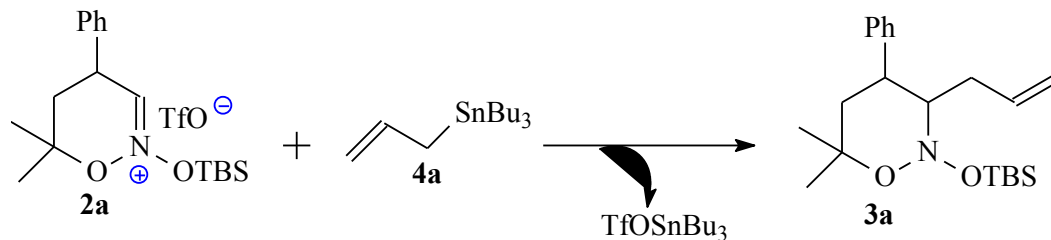
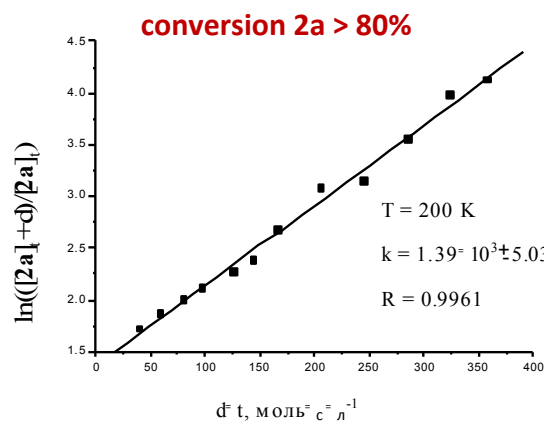
Реализация третьей ключевой стадии процесса *umprung*.



Kinetic investigation of nitronates C,C-coupling with nucleophiles.



Nu-E - π -nucleophile; Nu' – the fragment of nucleophile with transformed π -system; E – electrofug.



All couplings 2+4 have second-order kinetic.

The scale of reactivity (Prof. H. Mayr)

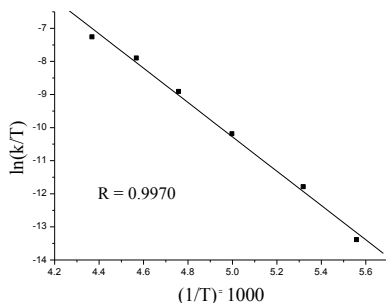
For 20° C: $\lg k = s (N+E)$ (H. Mayr et al. *JACS*, 2001, 123, 9500).

N – parameter of nucleophilicity (determined for referenced nucleophiles);

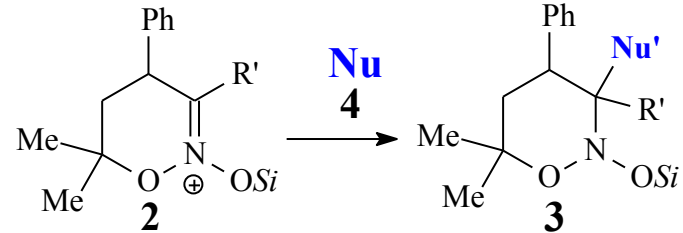
E – parameter of electrophilicity for cations 2;

s – factor of selectivity for 2+4 couplings;

k – speed constant for 2+4 coupling reactions



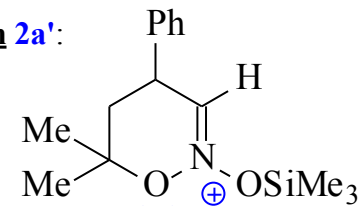
Parameters of electrophilicity (E) for iminium cations **2a** and **2b**.



Cation	R'	Si	Nu	Nu'	Product
2a	H	TBS	4a		3a
2a	H	TBS	4f		3a
2a	H	TBS	4g		3b
2a	H	TBS	4h		3c
2a'	H	TMS	4a		3a'
2a'	H	TMS	4b		3b'
2a'	H	TMS	4c		3d
2a'	H	TMS	4d		3c'
2b	Me	TBS	4e		3e

Cation	Nucleophile	Product	N (s)	E	k (20°C), l/mol·sec	ΔG^\ddagger kJ/mol	ΔH^\ddagger kJ/mol	ΔS^\ddagger J/mol·K
2a	4a	3a	5.46 (0.89)	-3.69	37.7	62.9 ± 3.7	42.9 ± 1.5	-68.1 ± 7.4
	4f	3a	3.09 (0.90)	-3.37	0.55	73.2 ± 4.0	49.5 ± 1.8	-80.7 ± 7.8
	4g	3b	5.13 (0.90)	-4.21	6.55	67.1 ± 4.4	45.2 ± 1.9	-74.9 ± 8.6
	4h	3c	6.22 (0.96)	-6.08	1.37	70.9 ± 1.7	51.1 ± 0.7	-67.6 ± 3.3
2a'	4a	3a'	5.46 (0.89)	-3.70	36.6	63.0 ± 3.6	41.7 ± 1.5	-72.4 ± 7.2
	4b	3b'	4.41 (0.96)	-4.54	0.74	72.4 ± 2.3	39.2 ± 1.0	-113.6 ± 4.4
	4c	3d	5.41 (0.91)	-5.45	0.92	71.9 ± 2.3	43.9 ± 1.0	-95.6 ± 4.3
	4d	3c'	6.22 (0.96)	-5.99	1.65	70.5 ± 1.7	51.7 ± 0.7	-64.1 ± 3.1
2b	4e	3e	10.32 (0.79)	-10.21	1.23	71.2 ± 1.1	31.4 ± 0.5	-135.9 ± 2.3

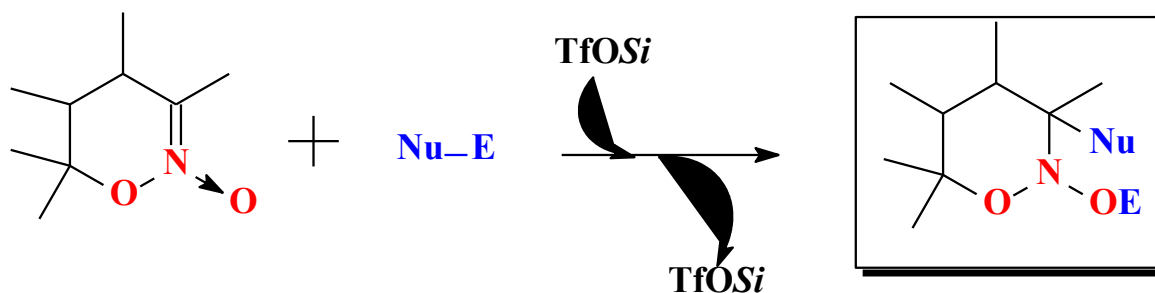
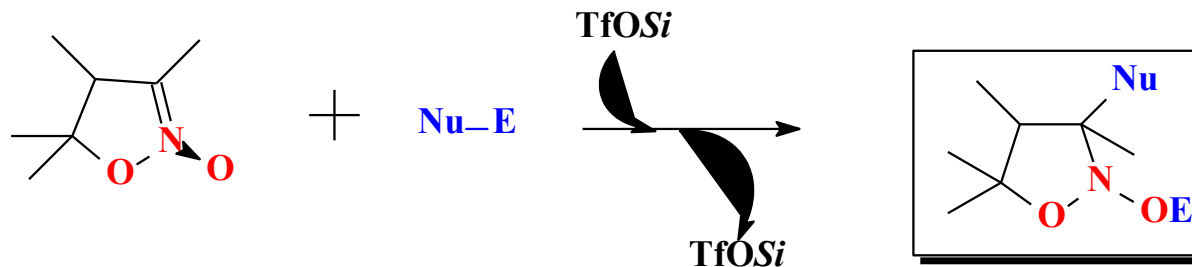
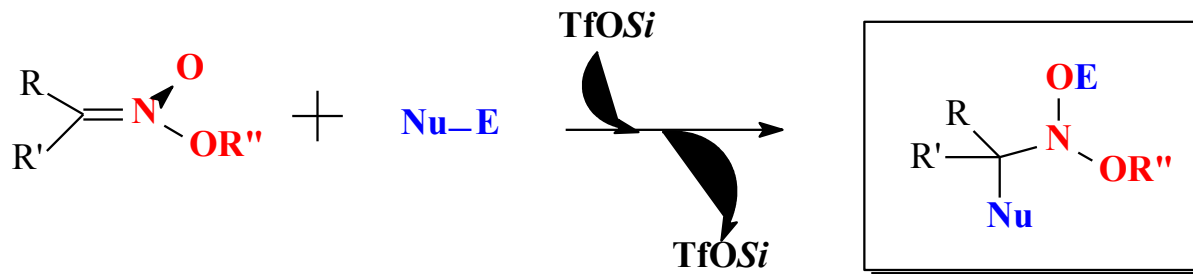
For cation **2a'**:



E from -3.37 to -6.08
(four points) 17

π -nucleophiles which have parameter $N > 4$ must react smoothly with cations **2** (R=H) by 200–240K

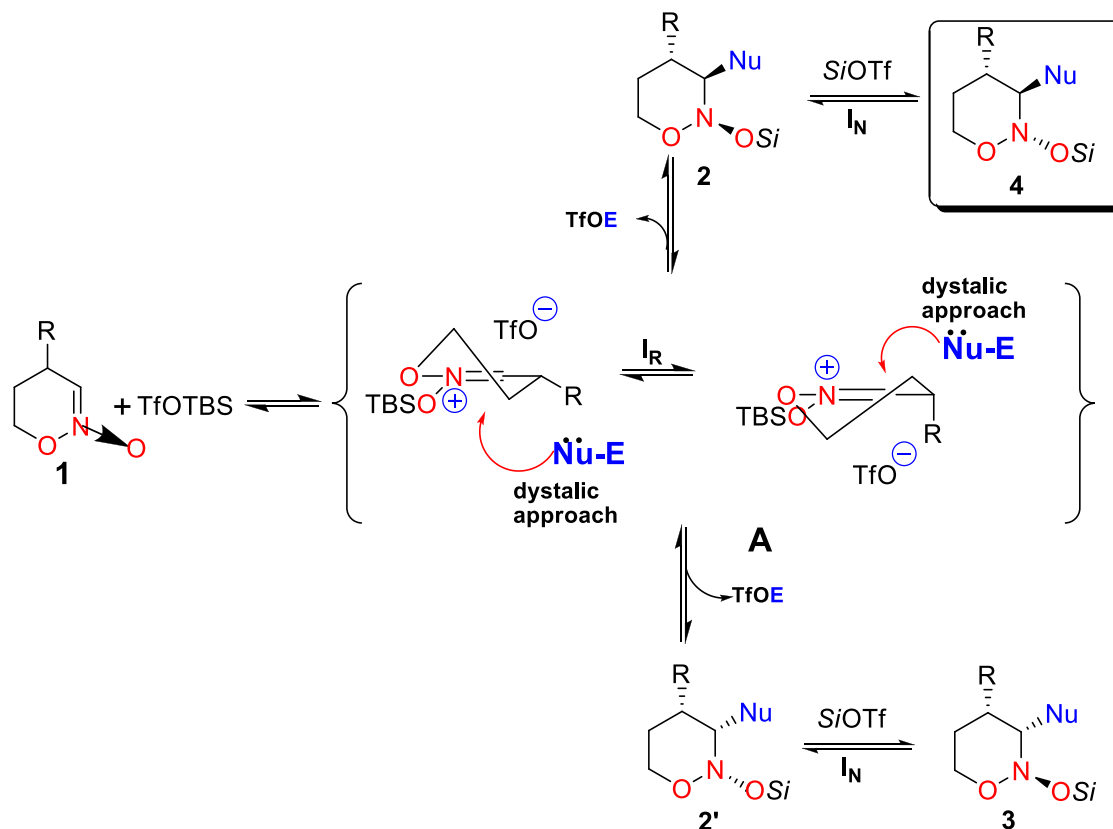
Область применения процесса, его универсальность.



Nu-E – C- or N-centered nucleophiles (silylketene acetals, silyl enolates, silyl amines or silyl ene-amines, silyl cyanides, trialkyl stannane; **E** – nucleofug (usually R₃Si-group); **R''** – alkyl or R₃Si.

Reversibility of C,N-coupling of six-membered cyclic nitronates with silylamines.

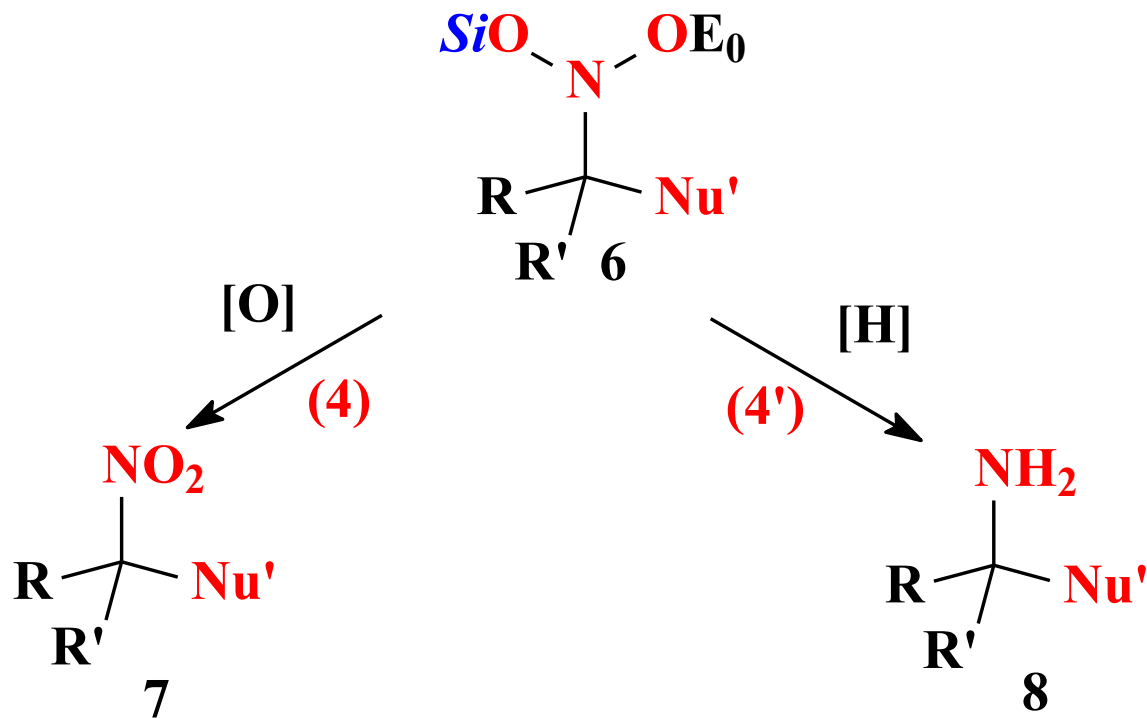
(EuroJOC, 2013, 5670)



При интерпретации стереохимических результатов C,N-сочетания нитронатов с нуклеофилами нужно учитывать, что этот процесс может быть обратимым.

Nu-E – silylamine; I_N – nitrogen inversion; I_R – ring inversion; **A** – the salt.

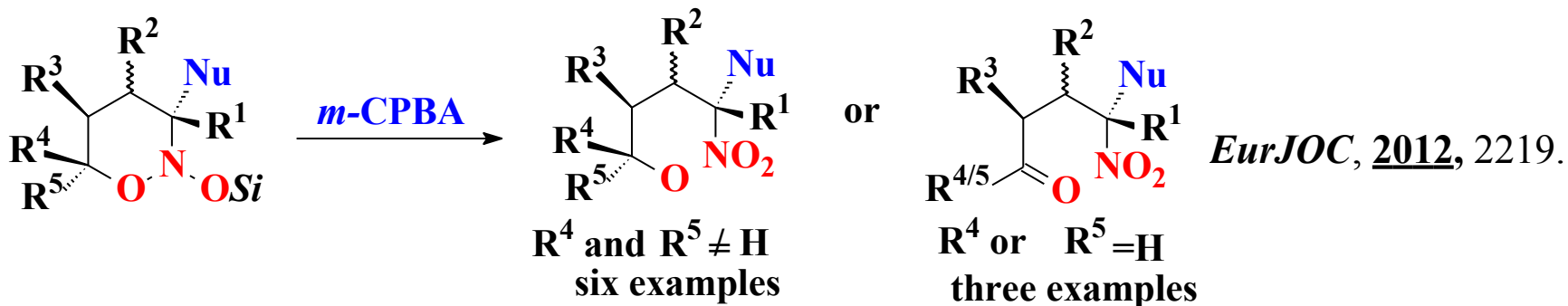
Реализация финальных стадий процесса.



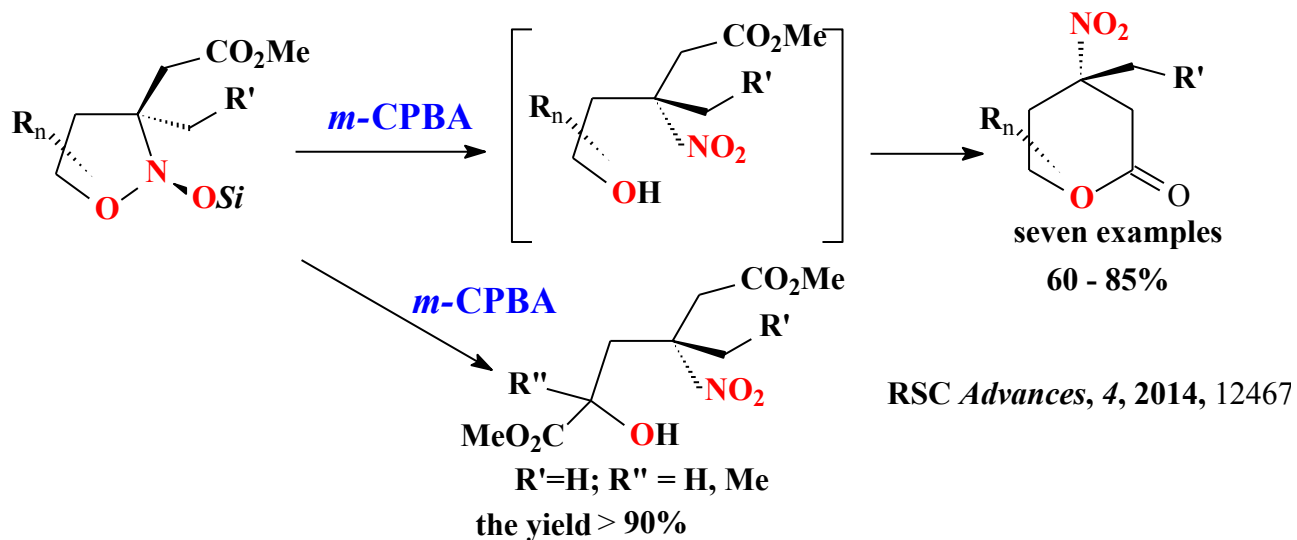
The oxidation of nitrosoacetals.



V.F. Rudchenko et al., *Rus Chem. Bull.*, **1983**, 1578.



the yield > 80%, *dr* > 10



The reduction of nitrosoacetals.

