Unsaturated Fluorine-containing α-Amino Acids: Synthesis and Application in Metal Catalysis

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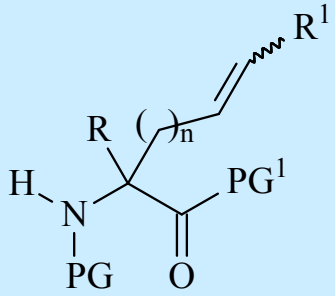
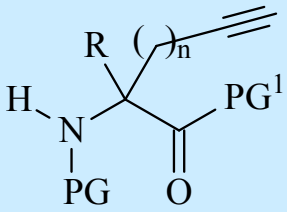
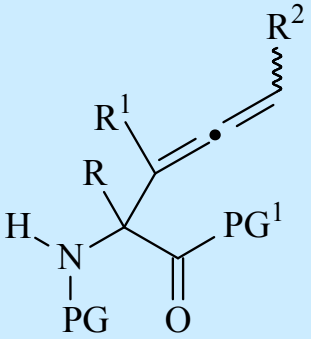
INEOS, Ecological Chemistry Team

Non-proteinogenic Unsaturated α-Amino Acids

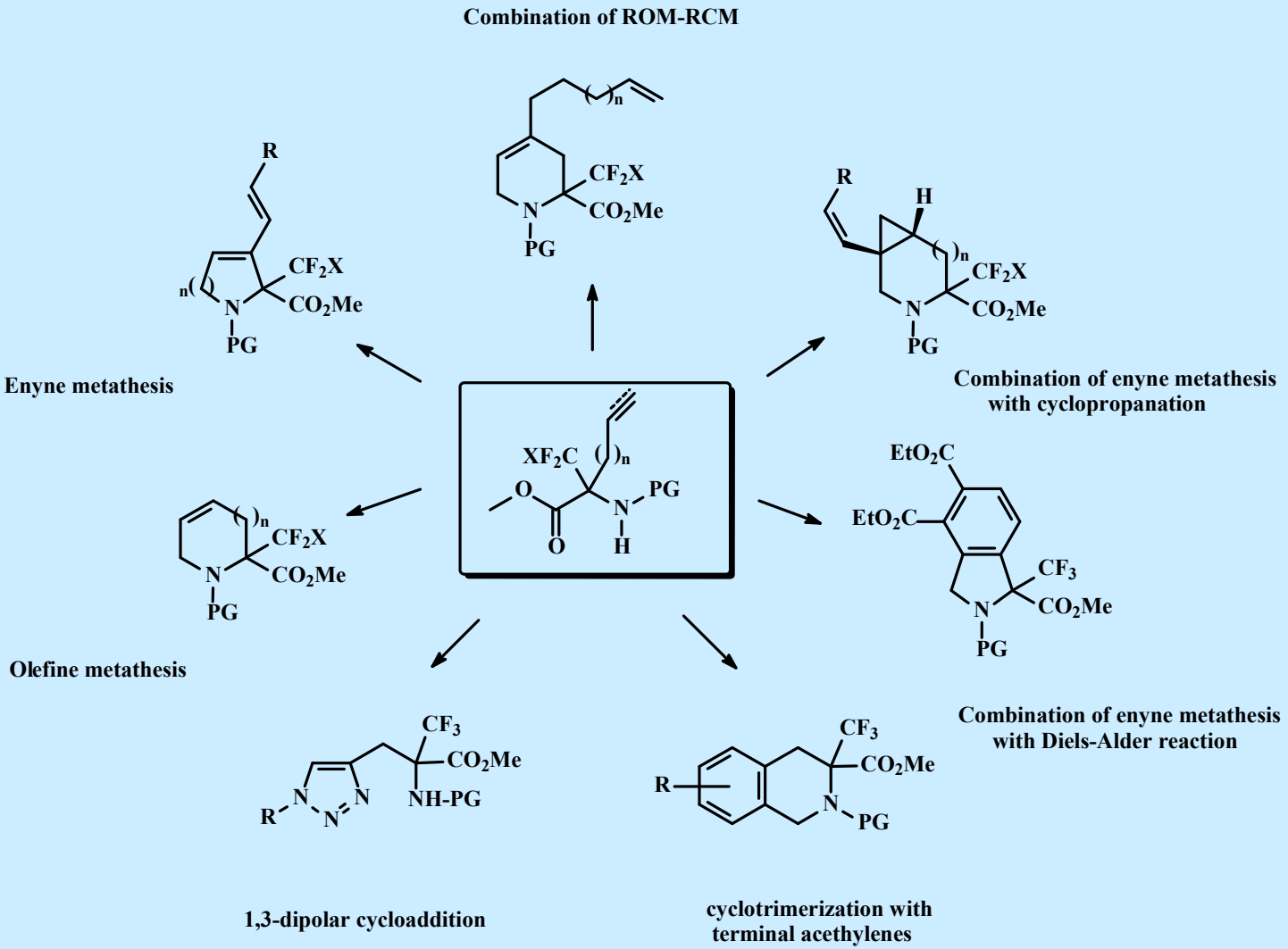




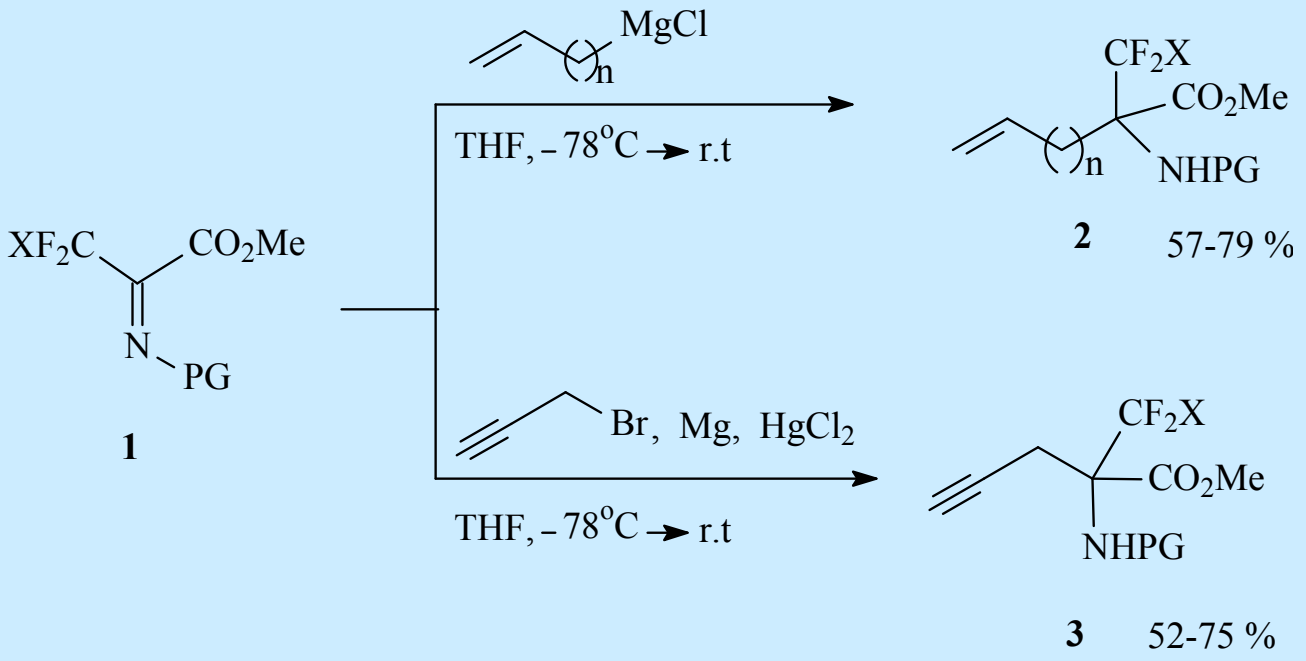


- Modifications of the side chain;
- Direct cyclisations of the amino acids;
- Cyclisations of side chain *via* a substituent on the nitrogen atom;
- Cyclisations making use of the ester substituent and the side chain.

Metal-catalyzed transformations of fluorine-containing unsaturated α-amino acids



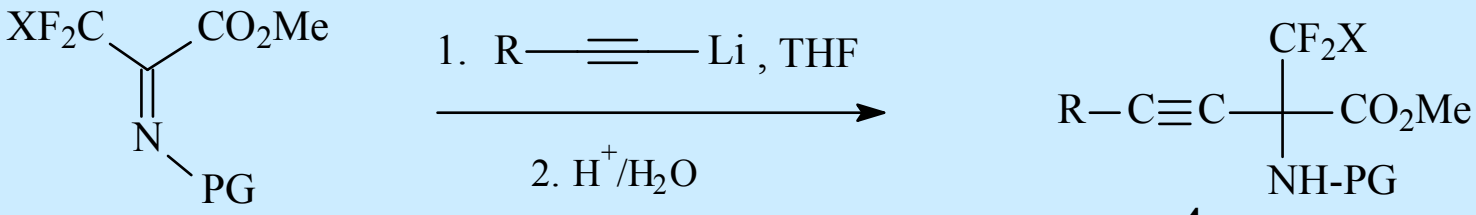
Synthesis of unsaturated α-CF_2X-α-amino acid derivatives



X = F, Cl; n = 0, 1, 2; PG = Cbz, Boc, Ts, SO_2Ph, CO_2Et

S.N. Osipov, A.S. Golubev, N. Sewald, T. Michel,
A.F. Kolomiets, A.V. Fokin, K. Burger, *J. Org. Chem.*, **1996**, 7521

Synthesis of acethylenic α-CF_2X-α-amino acid derivatives

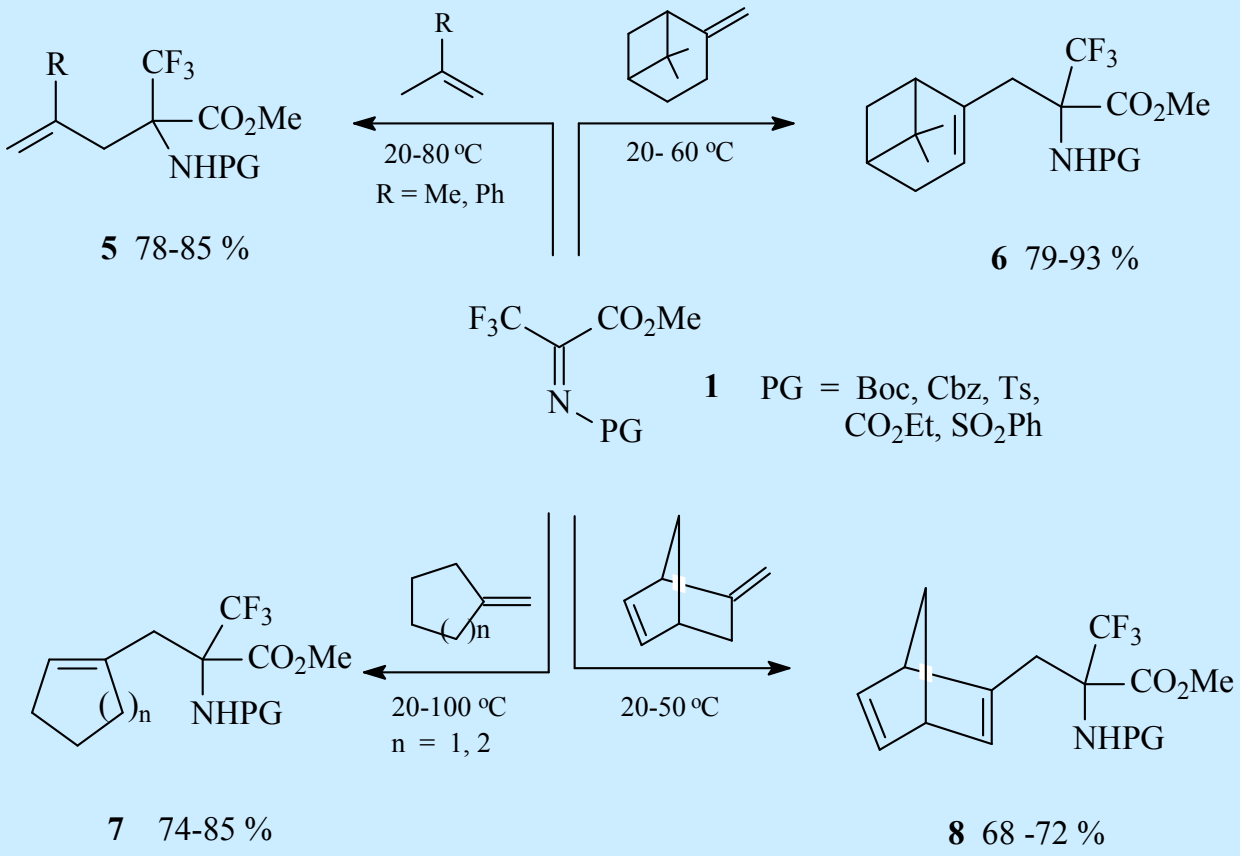


4

Product	X	R	PG	Yield, %
4a	F	H	SO_2Ph	61
4b	Cl	H	Cbz	65
4b	Cl	H	Boc	50
4c	F	n-Bu	Cbz	52
4d	F	CH_2OMe	Cbz	60
4e	F	cyclopropyl	Cbz	55
4f	F	$C(Me)=CH_2$	Ts	38

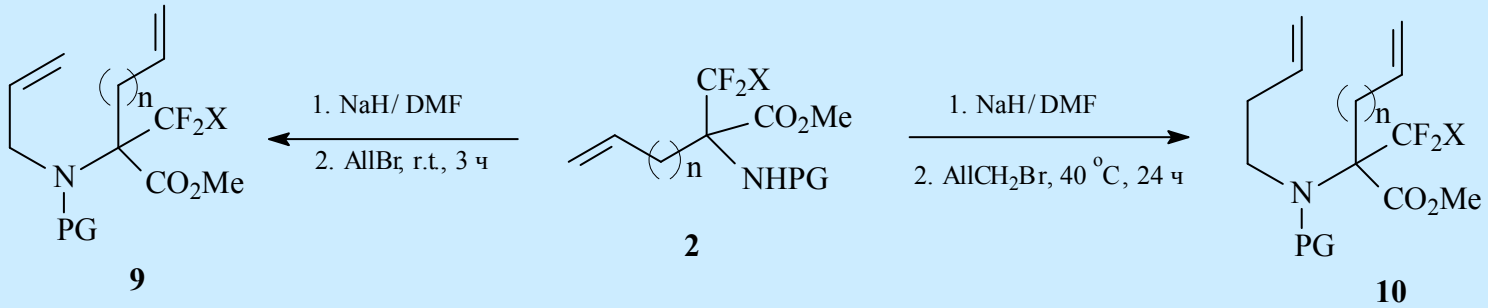
D. Semeril, J. Le Notre, C. Bruneau, P.H. Dixneuf, A.F. Kolomiets, S.N. Osipov, *New J. Chem.*, **2001**, 130

Unsaturated α-Amino Acids *via* Imino-ene Reaction



N.M.Kobel'kova, S.N. Osipov, A.F. Kolomiets, *Russ. Chem. Bull.*, **2001**, *6*, 997

Precursors for Ring Closing Olefine Metathesis

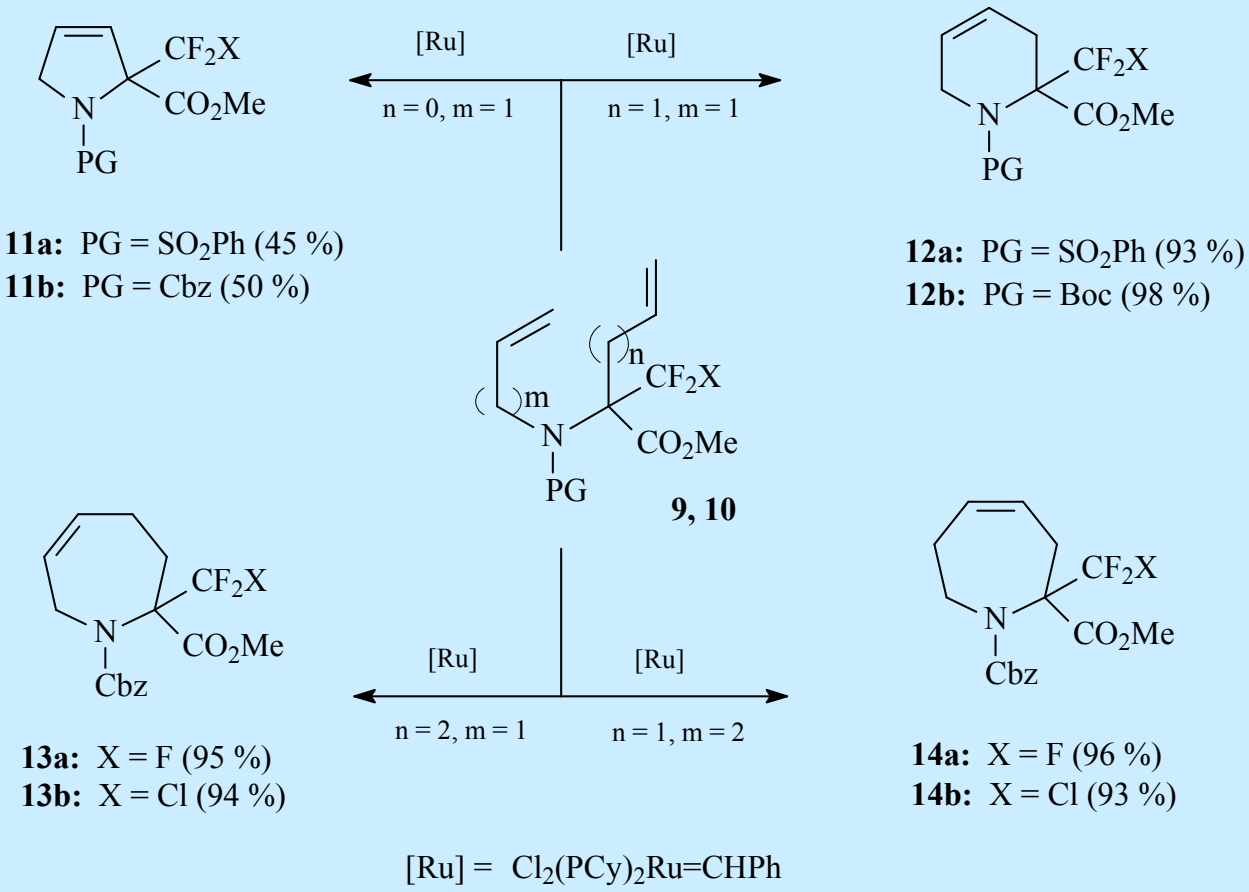


9 **2** **10**

Product	n	X	PG	Yield, %
9a	0	F	SO_2Ph	81
9b	0	F	Cbz	65
9c	1	F	SO_2Ph	72
9d	1	F	Boc	55
9e	2	F	Cbz	67
9f	2	F	Boc	69
9g	2	Cl	Cbz	61
10a	1	F	Cbz	53
10b	1	Cl	Cbz	51

S.N. Osipov, C. Bruneau, M. Picquet, A.F. Kolomiets, P.H. Dixneuf, *Chem. Commun*., **1998**, 2053

Ring Closing Olefine Metathesis



11a: PG = SO_2Ph (45 %)
11b: PG = Cbz (50 %)

12a: PG = SO_2Ph (93 %)
12b: PG = Boc (98 %)

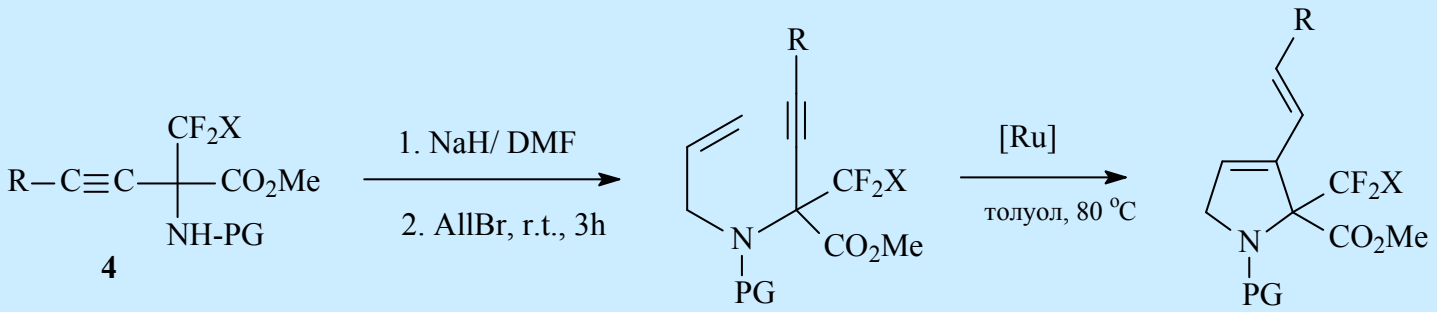
13a: X = F (95 %)
13b: X = Cl (94 %)

14a: X = F (96 %)
14b: X = Cl (93 %)

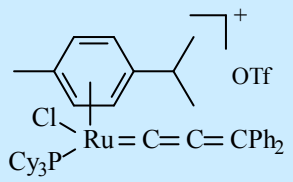
[Ru] = $Cl_2(PCy)_2Ru{=}CHPh$

S.N. Osipov, O.I. Artyushin, A.F. Kolomiets, C. Bruneau, M. Picquet, P.H. Dixneuf, *Eur. J. Org. Chem.*, **2001**, *20*, 3891.

Ring Closing Enyne Metathesis



[Ru] = $Cl_2(PCy)_2Ru{=}CHPh$ **(A)** ,

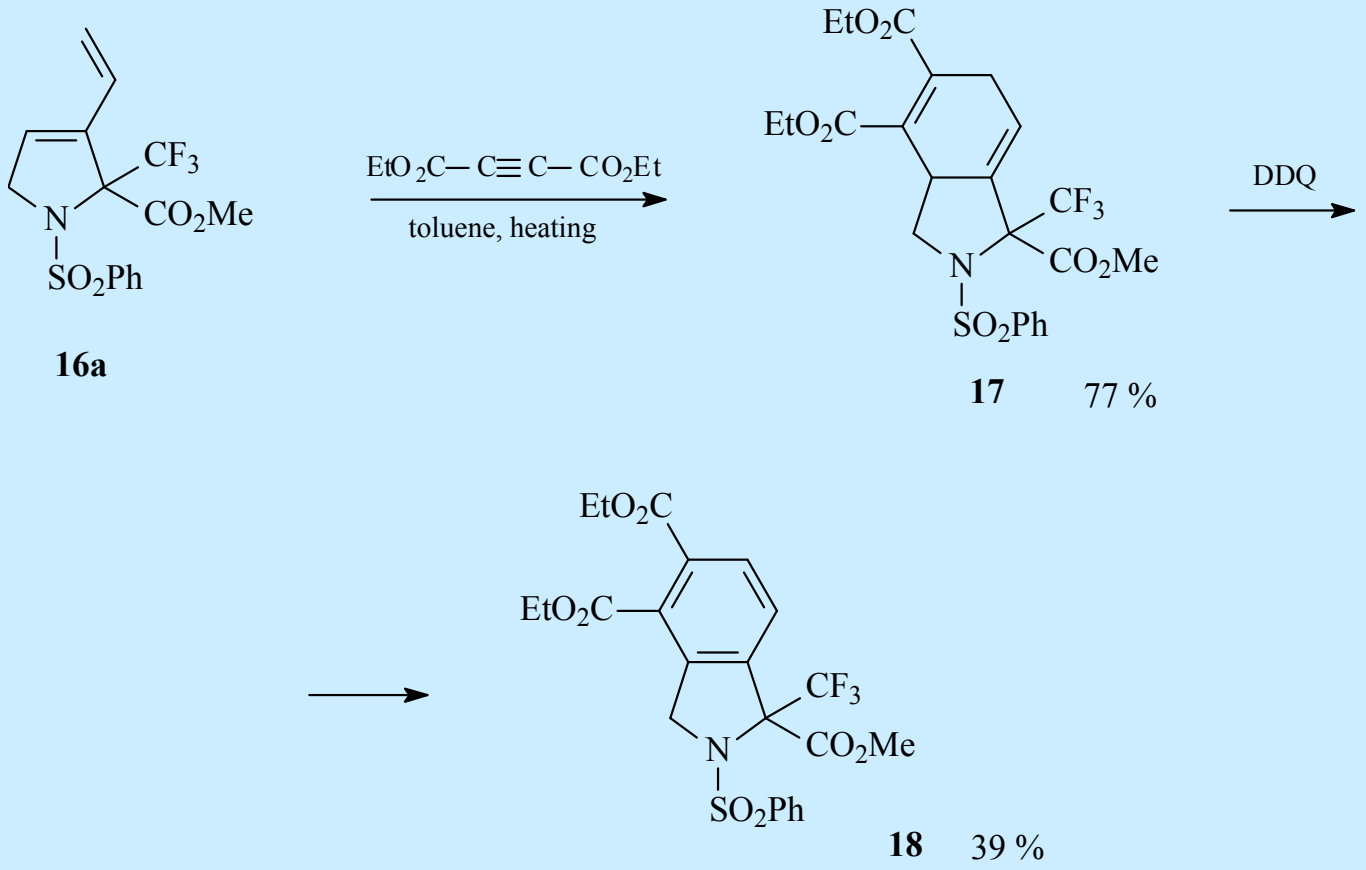


(B)

соединение	X	R	PG	Cat	Выход, %
16a	F	H	SO_2Ph	A/B	65/70
16b	Cl	H	Boc	A/B	50/56
16c	F	n-Bu	Cbz	B	40
16d	F	CH_2OMe	Cbz	B	14

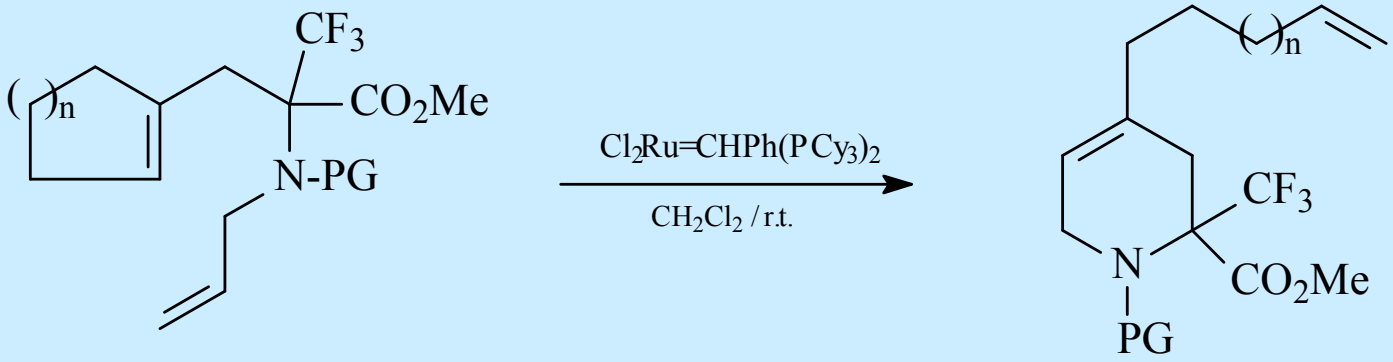
D. Semeril, J. Le Notre, C. Bruneau, P.H. Dixneuf, A.F. Kolomiets, S.N. Osipov, *New J. Chem.*, **2001**, 16.

Synthesis of bicyclic α-CF_3-proline derivatives



D. Semeril, J. Le Notre, C. Bruneau, P.H. Dixneuf, A.F. Kolomiets, S.N. Osipov, *New J. Chem.*, **2001**, 16

Combination of Intramolecular Ring Opening – Ring Closing Metathesis



19

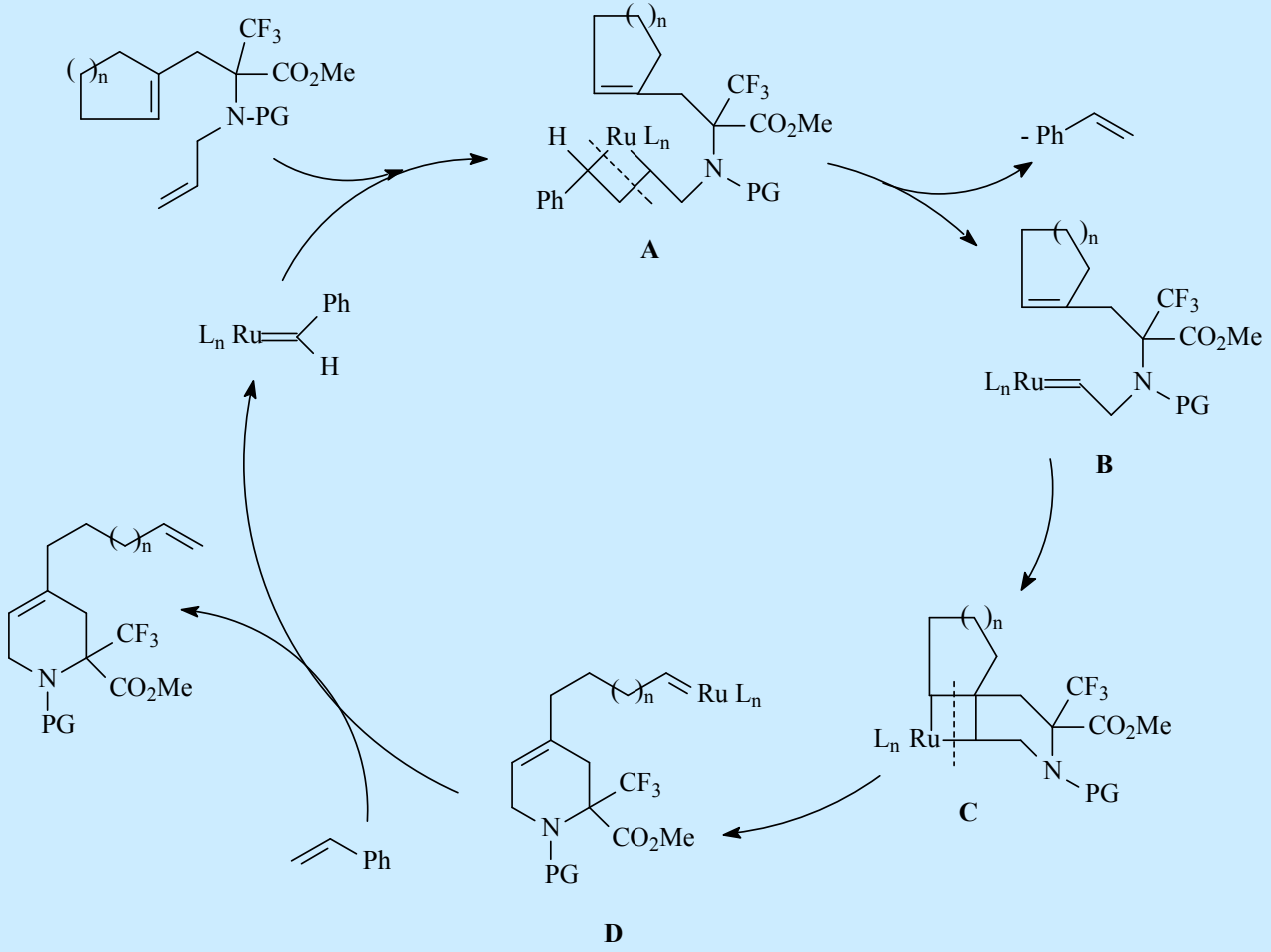
20 74 - 86 %

PG=SO_2Ph, SO_2Me, Boc

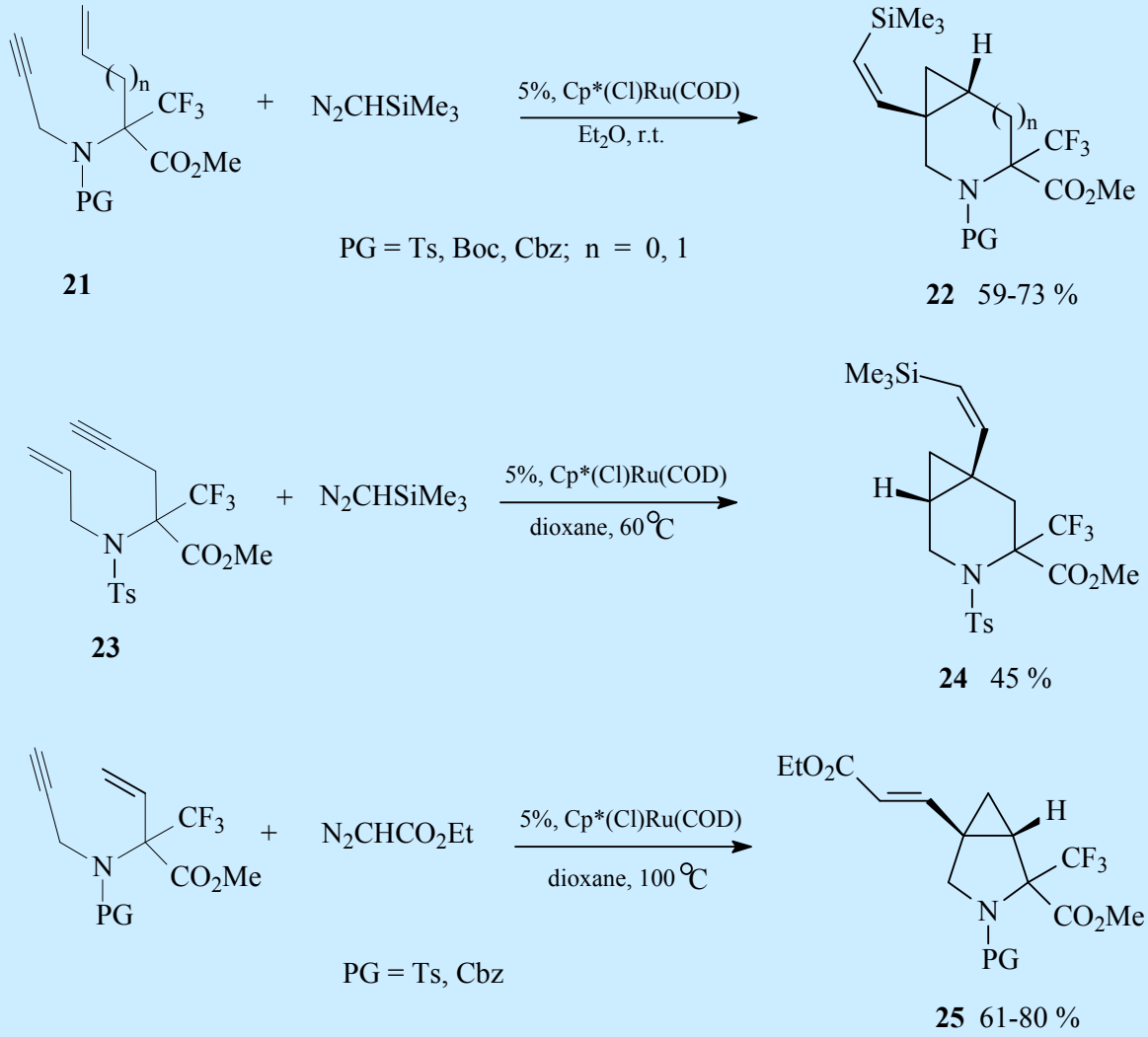
n = 1, 2

S.N. Osipov, N.M. Kobel'kova, G.T. Shchetnikov, A.F. Kolomiets, C. Bruneau, P.H. Dixneuf, *Synlett*, **2001**, 621.

Proposed Mechanism of ROM-RCM

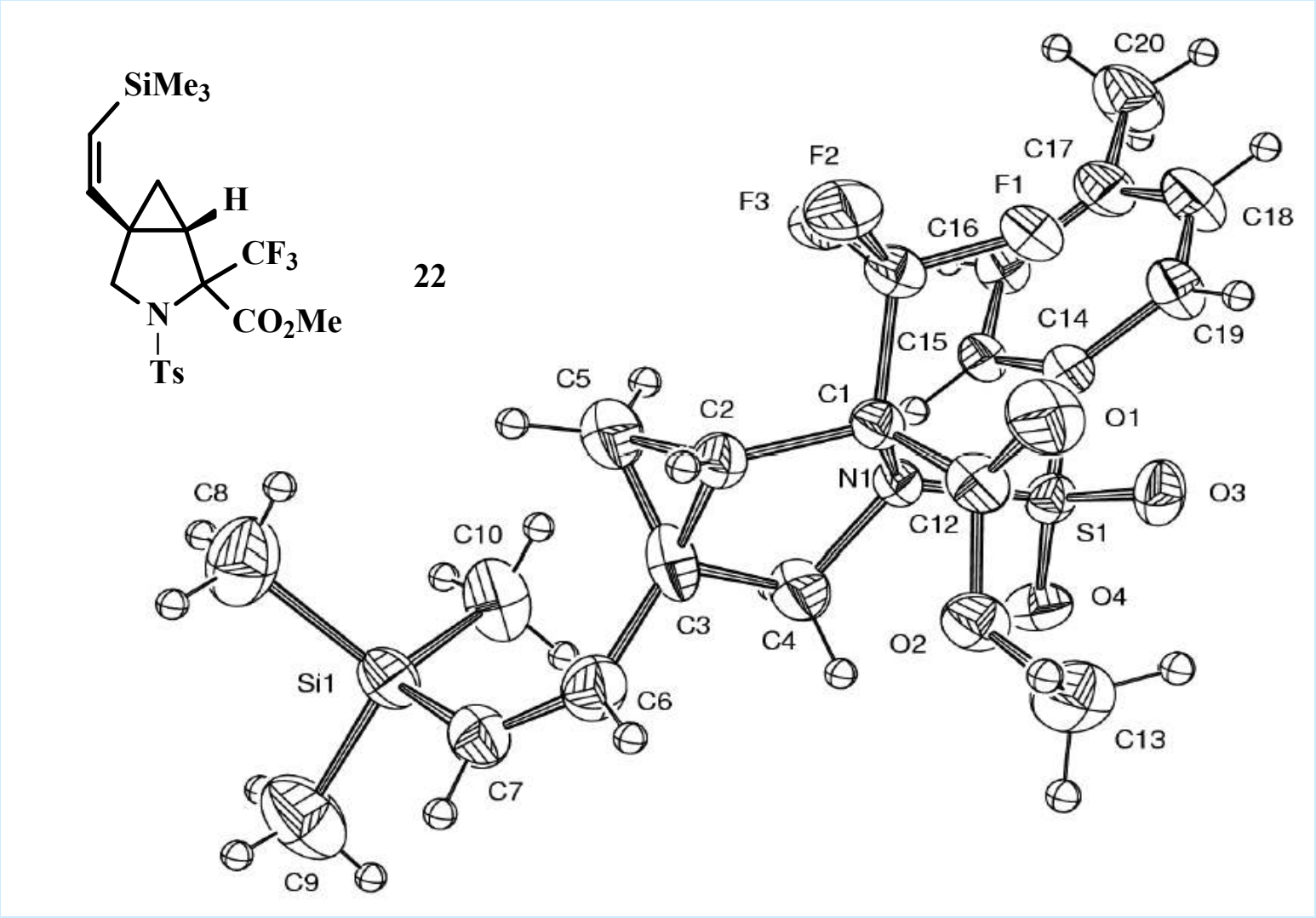


Tandem Catalytic Carbene Addition – Bicyclization of Enynes

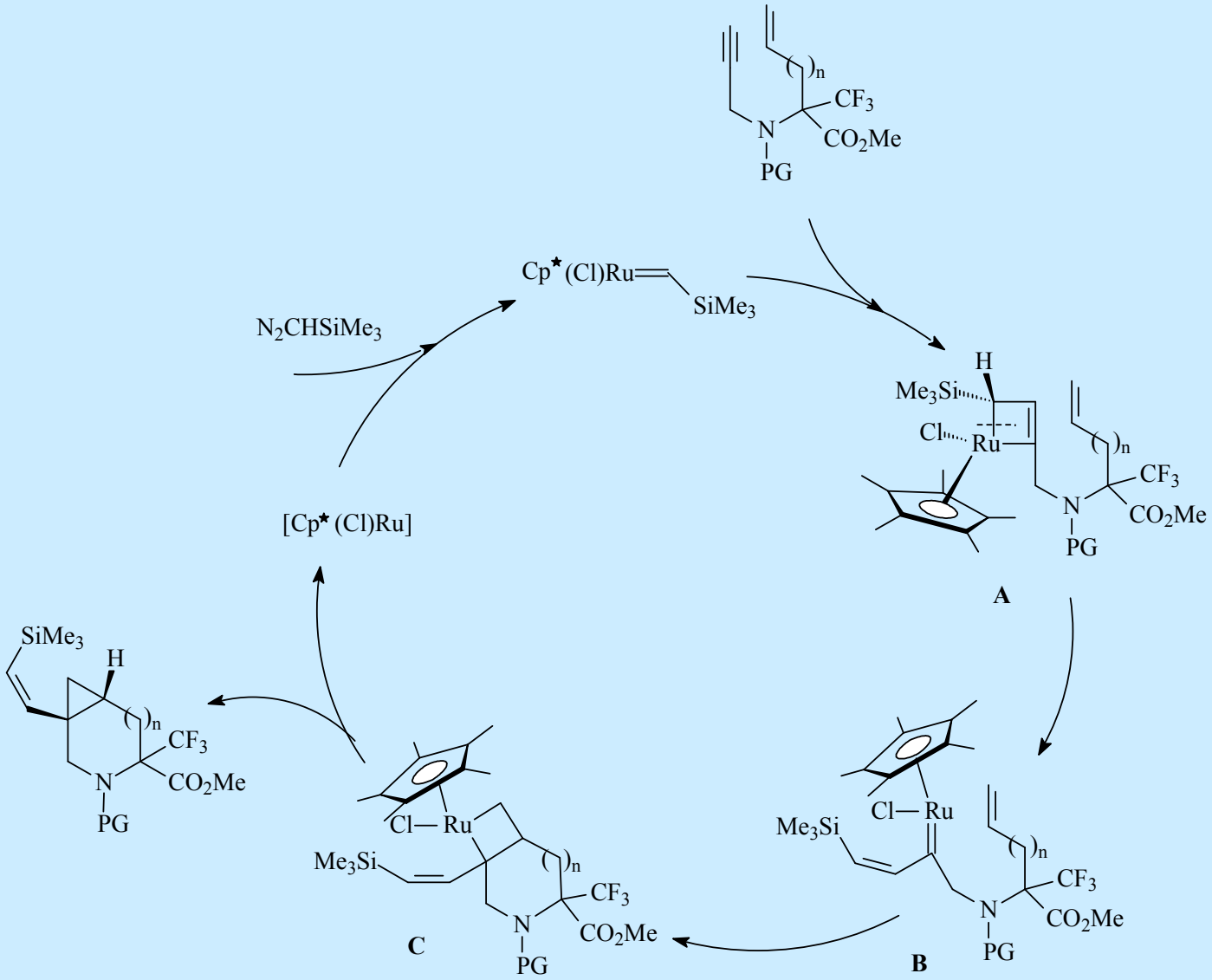


F.Monnier, G.T. Shchetnikov, I.D. Titanyuk, S.N. Osipov, S. Derrien, P.H. Dixneuf, *Org. Lett*, **2005**, 3741.

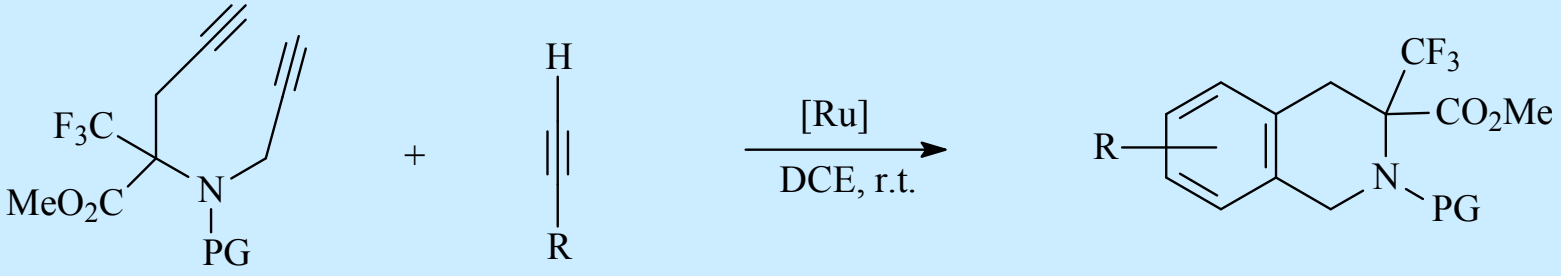
RSA of Compound 22 (n = 0, PG = Ts)



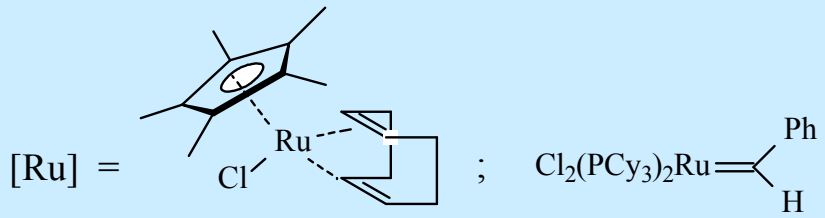
Proposed Mechanism of Ru-catalyzed Tandem Carbene Addition – Bicyclization



Cyclotrimerization of 1,7-diynes with terminal acethylenes



26 **27**



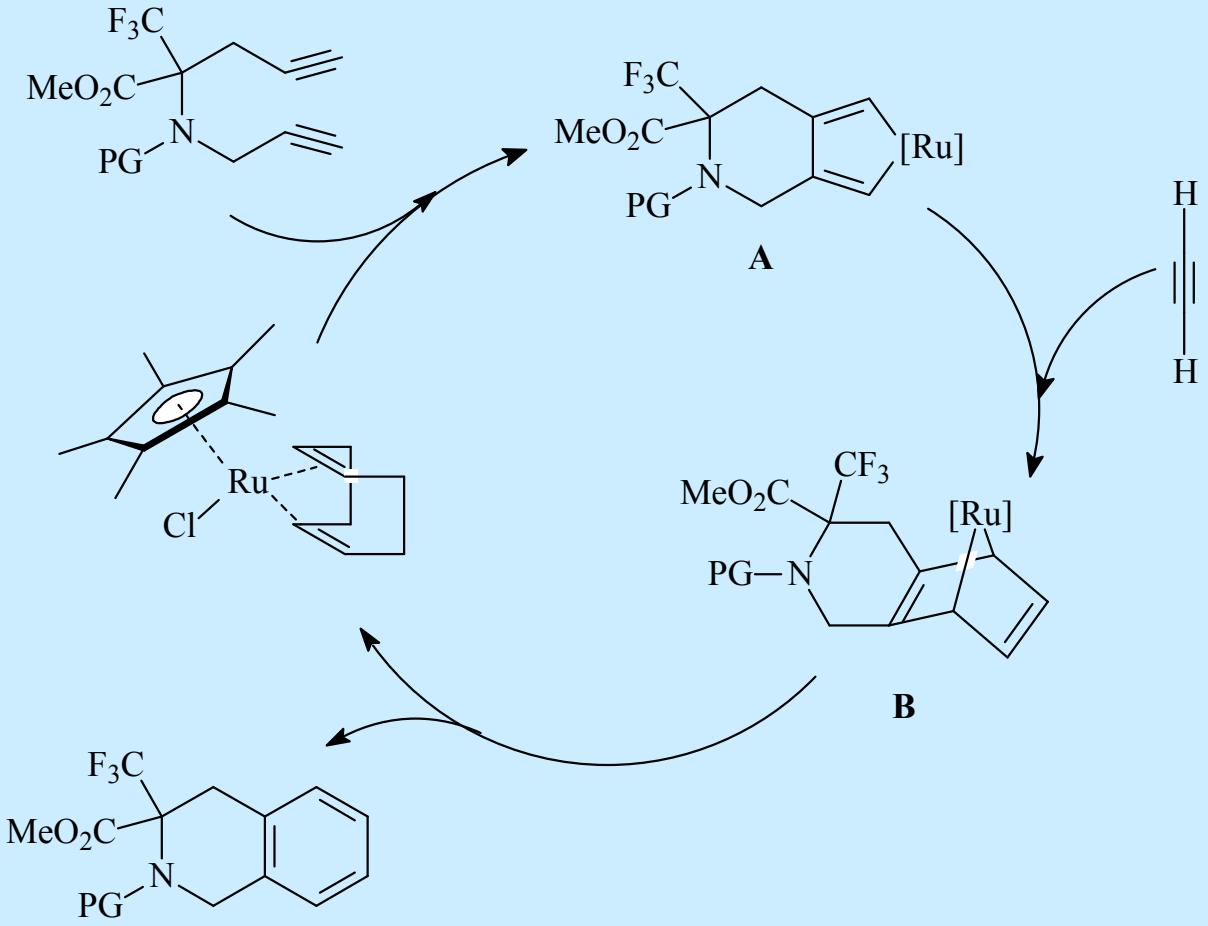
A **B**

№	PG	R	Product	Cat A/B	Yield, %
1	SO_2Ph	H	**27a**	A/B	94/81
2	SO_2Ph	C_4H_9	**27b**	A	92
3	SO_2Ph	C_6H_{13}	**27c**	A	89
4	Cbz	H	**27d**	A/B	96/75

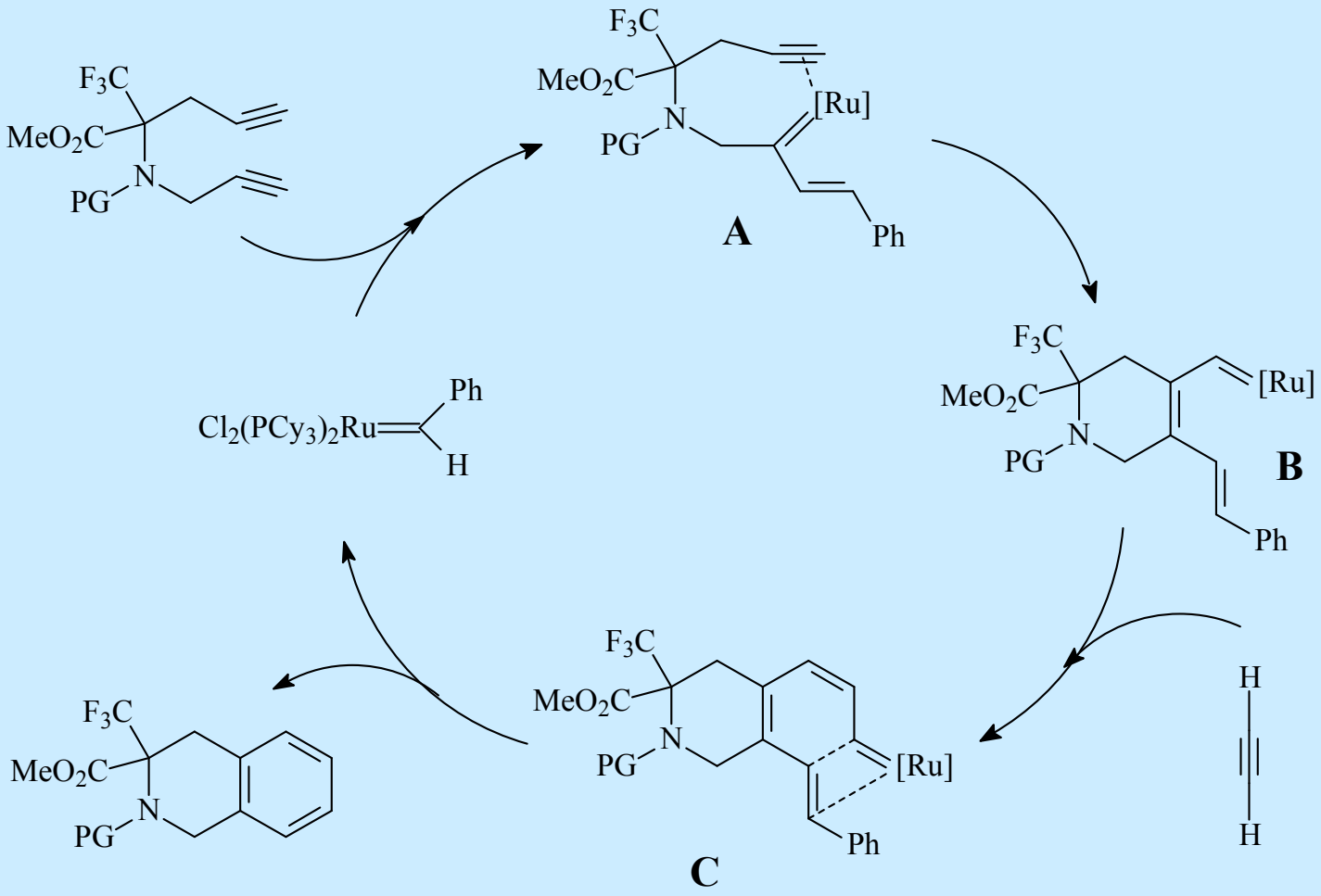
№	PG	R	Product	Cat A/B	Yield, %
5	Cbz	C_4H_9	**27e**	A	85
6	Boc	H	**27f**	A/B	89/70
7	Boc	C_4H_9	**27g**	A/B	82/65

S.N. Osipov, G.T., Shchetnikov, P.H. Dixneuf, Tetrahedron Lett., **2006**, submitted.

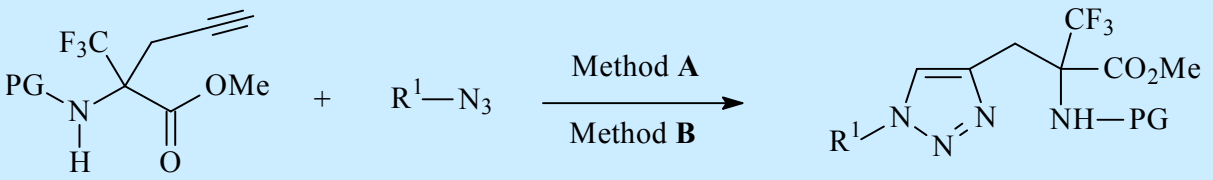
Mechanism of Cyclotrimerization catalyzed by Cp*Ru(COD)Cl



Proposed Mechanism of Cyclotrimerization catalyzed by $Cl_2(PCy)_2Ru=CHPh$

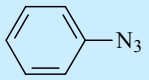
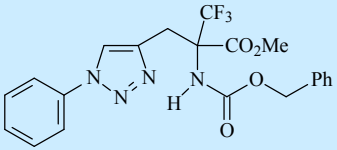
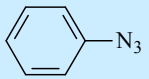
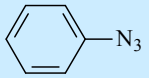
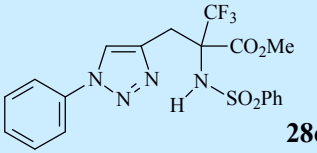
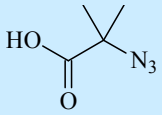
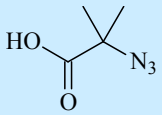
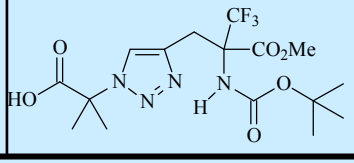


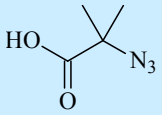
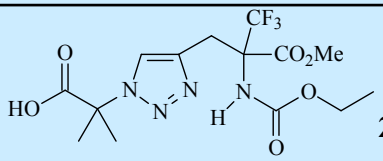
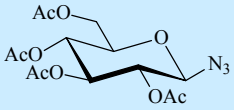
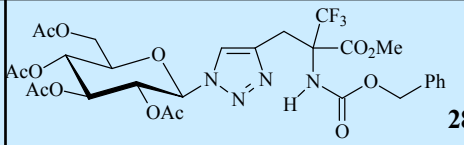
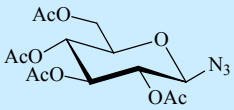
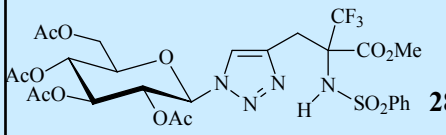
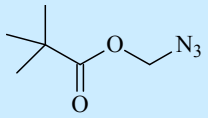
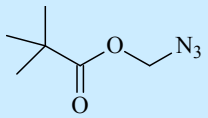
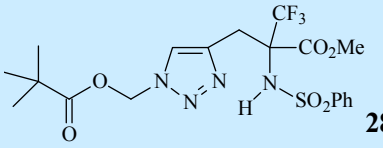
1, 3-Dipolar Cycloaddition to Organic Azides



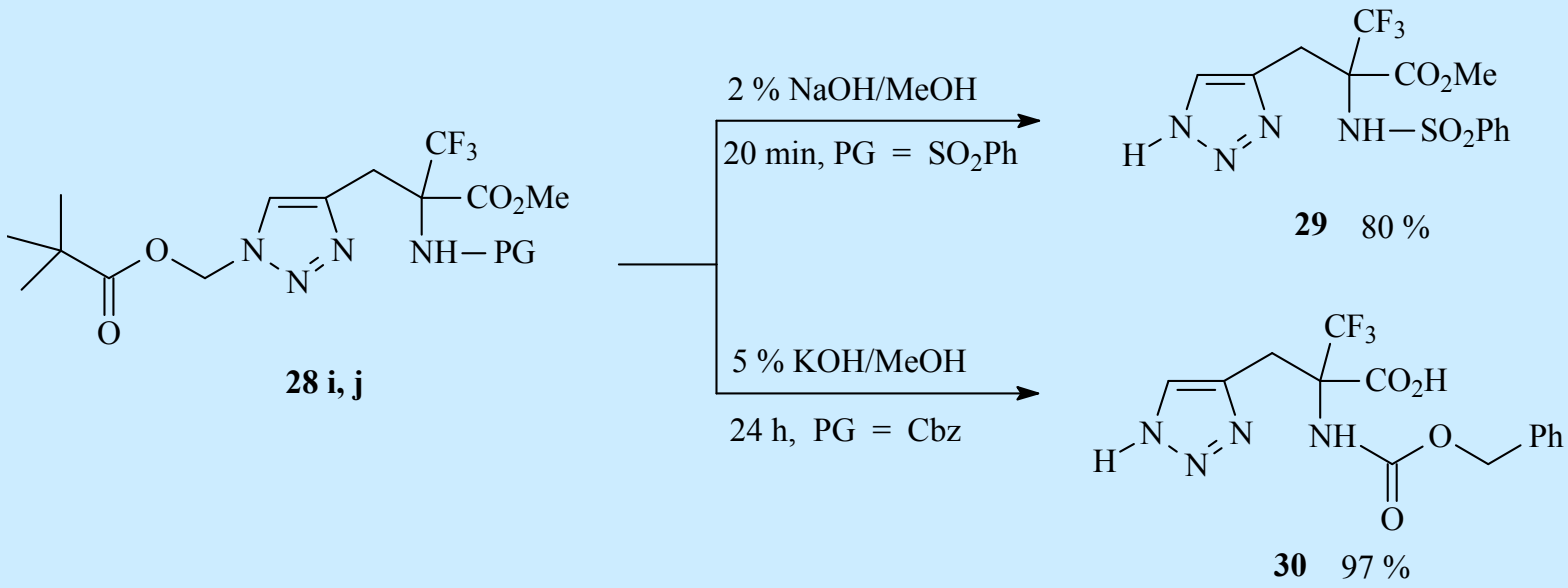
28

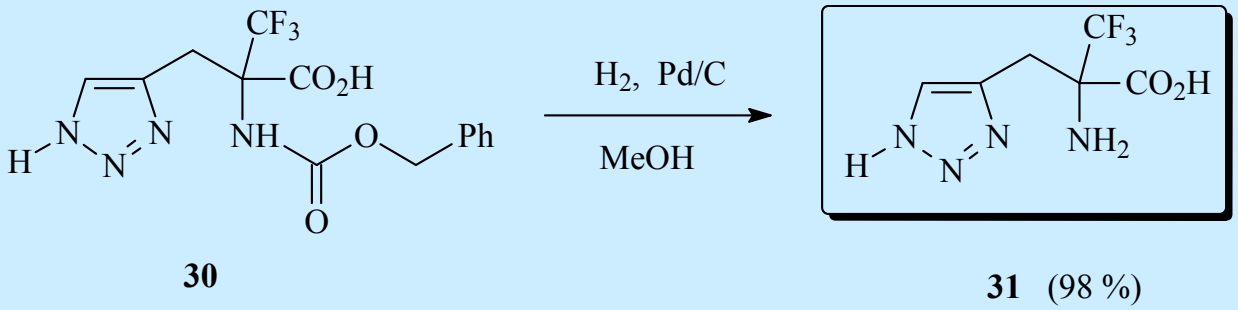
Method A : CuI (5 mol%), DIPEA, THF;
Method B : $CuSO_4$ (3 mol%), Na-ascorbate (5 mol%), H_2O/t-BuOH

№	R^1-N_3	Method	Product
1		**A**	 **28a** (91 %)
2		**A**	 **28b** (93 %)
3		**A/B**	 **28c** (86/91 %)
4		**A**	 **28d** (94 %)
5		**B**	 **28e** (88 %)

№	R^1-N_3	Method	Product
6		**A/B**	 **28f** (87/90 %)
7		**B**	 **28g** (87 %)
8		**B**	 **28h** (84 %)
9		**A/B**	 **28i** (84/94 %)
10		**B**	 **28j** (92 %)

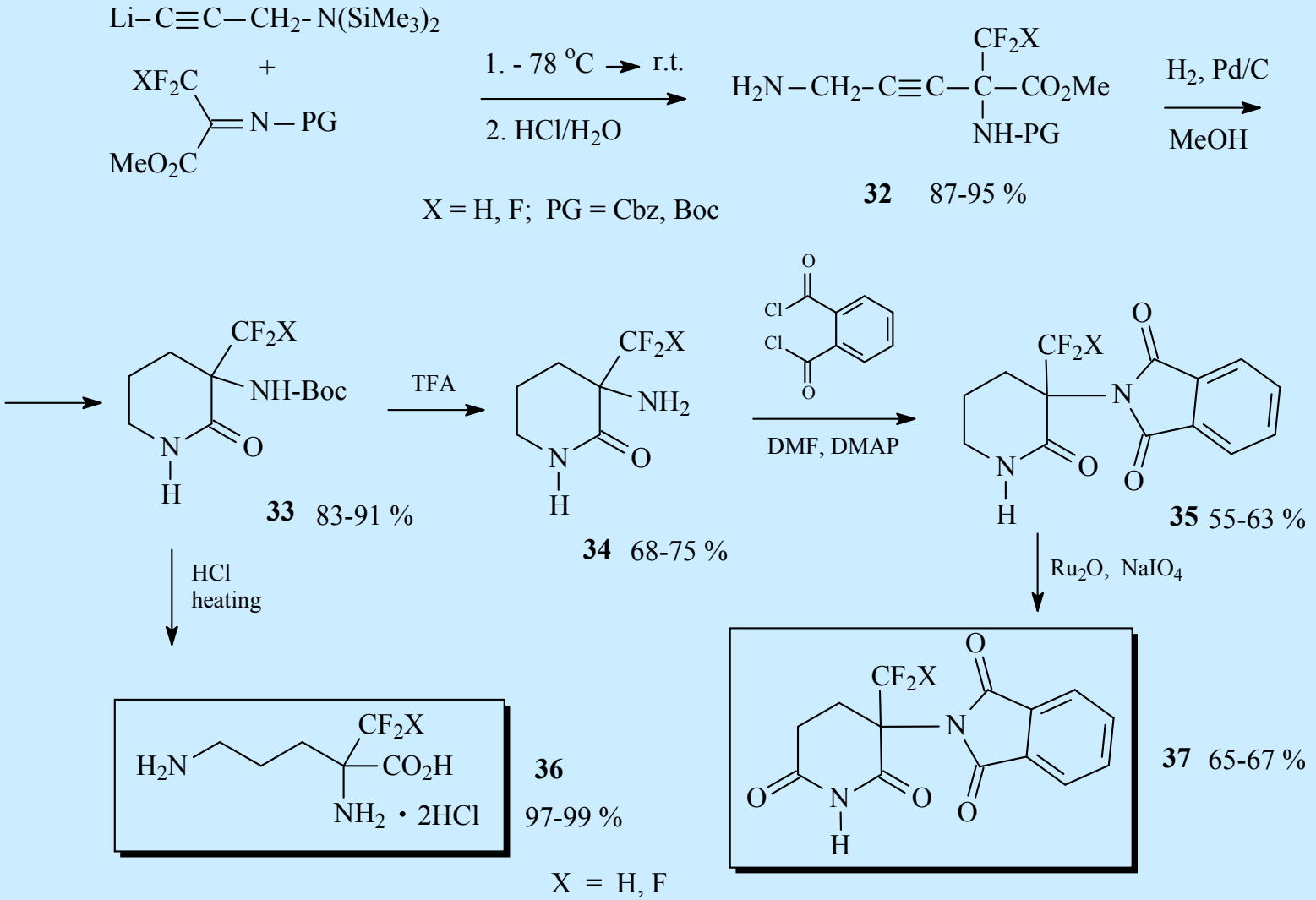
Synthesis of α-CF_3-Histidine Aza-analog





G.T. Shchetnikov, A.S. Peregudov, S.N. Osipov, *Synlet*, **2006**, submitted

Synthesis of α-CF_2X-substituted Ornithines and Thalidomides



S.N. Osipov, A.S. Golubev, N. Sewald, K. Burger, *Tetrahedron Letters* **1997,** 5965.
S.N. Osipov, P. Tsouker, L. Hennig, K. Burger, *Tetrahedron*, **2004**, 271

Acknowledgment

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- Dr. I.D. Titanyuk

Dr. A.F. Kolomiets

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- Dr. Ch. Bruneau

University of Leipzig (Germany):

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- RFBR N 03-03-22000