Palladium-Catalyzed Cross-Couplings in Organic Synthesis

2010 Nobel Prize in Chemistry

Professor Sambasivarao Kotha

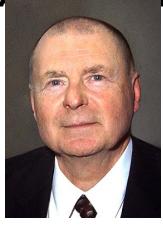
Department of Chemistry IIT-Bombay 400 076 http/www.chem.iitb.ac.in/~srk

THE NOBEL PRIZE IN CHEMISTRY 2010



"palladium-catalyzed cross couplings in organic synthesis"

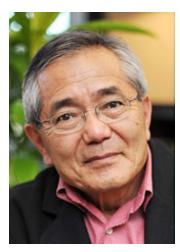
Richard F. Heck



University of Delaware USA

B 1931

Ei-ichi Negishi



Purdue University West Lafayette IN, USA B 1935

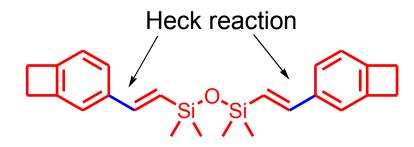


Hokkaido University Sapporo, Japan

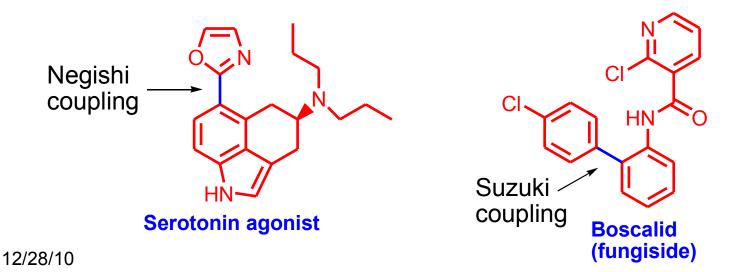
B 1930

12/28/10

Heck, Negishi and Suzuki coupling in synthesis of fine chemicals



DVS-bis-BCM (electronic resin monomer)



Facts on the Nobel Prize in Chemistry

On 27 November 1895, Alfred Nobel signed his last will and testament, giving the largest share of his fortune to a series of prizes, the Nobel Prizes. As described in Nobel's will one part was dedicated to " the person who shall have made the most important chemical discovery or improvement".

Number of Nobel Prizes in Chemistry

102 Nobel Prizes in Chemistry have been awarded since 1901. It was not awarded on eight occasions: in 1916, 1917, 1919, 1924, 1933, 1940, 1941 and 1942.

Why were the Chemistry Prizes not awarded in those years? In the statutes of the Nobel Foundation it says: "<u>If none of</u> <u>the works under consideration is found to be of the</u> <u>importance indicated in the first paragraph, the prize money</u> <u>shall be reserved until the following year</u>. If, even then, the prize cannot be awarded, the amount shall be added to the Foundation's restricted funds." During World War I and II, fewer Nobel Prizes were awarded.

Number of shared and unshared Nobel Prizes in Chemistry

62 Chemistry Prizes have been given to 1 Laureate only.22 Chemistry Prizes have been shared by 2 Laureates.18 Chemistry Prizes have been shared between 3 Laureates

Why is that? In the statutes of the Nobel Foundation it says: "A prize amount may be equally divided between two works, each of which is considered to merit a prize. If a work that is being rewarded has been produced by two or three persons , the prize shall be awarded to them jointly. In no case may a prize amount be divided between more than three persons."

Youngest Chemistry Laureate

"in recognition of their synthesis of new radioactive elements"

To date, the youngest Nobel Laureate in Chemistry is Frédéric Joliot, who was 35 years old when he was awarded the Chemistry Prize in 1935, together with his wife, Irène Joliot-Curie.

Oldest Chemistry Laureate

"for the development of methods for identification and structure analyses of biological macromolecules"

The oldest Nobel Laureate in Chemistry to date is John B. Fenn, who was 85 years old when he was awarded the Chemistry Prize in 2002.

Multiple Nobel Laureates in Chemistry

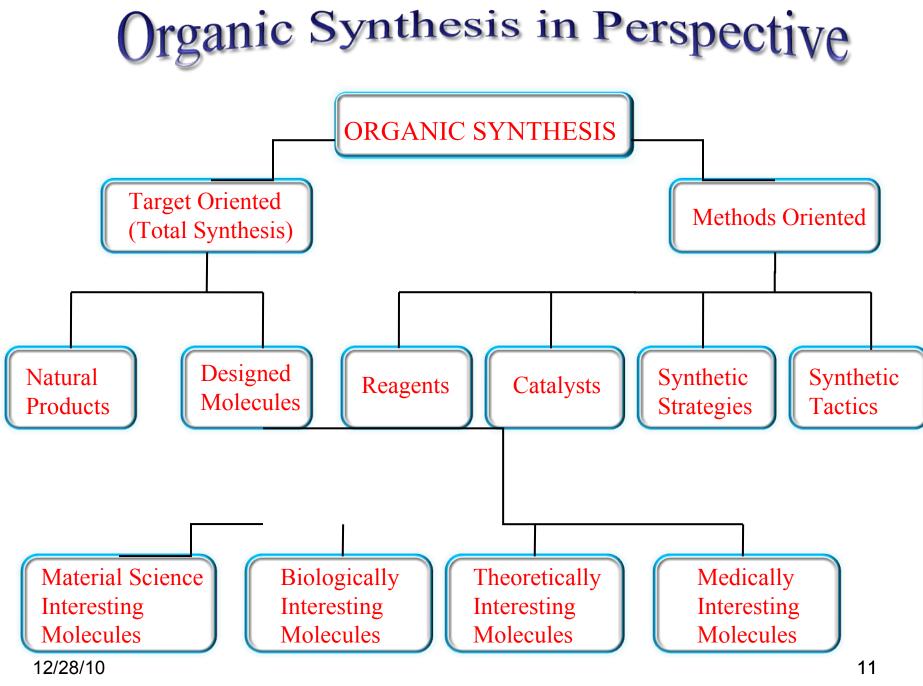
- Marie CurieLinus PaulingFrederick SangerPhysics 1903Chemistry 1954Chemistry 1958Chemistry 1911Peace 1962Chemistry 1980
- Linus Pauling is the only person who have been awarded two unshared Nobel Prizes.

Family Nobel Laureates in Chemistry

The Curies were the most successful "Nobel Prize family". The husband-and-wife partnership of Marie Curie and Pierre Curie were awarded the 1903 Nobel Prize in Physics. Marie Curie herself was awarded the Nobel Prize a second time, receiving the 1911 Nobel Prize in Chemistry. Marie and Pierre Curie's daughter, Irène Joliot-Curie, was awarded the 1935 Nobel Prize in Chemistry, together with her husband, Frédéric Joliot.

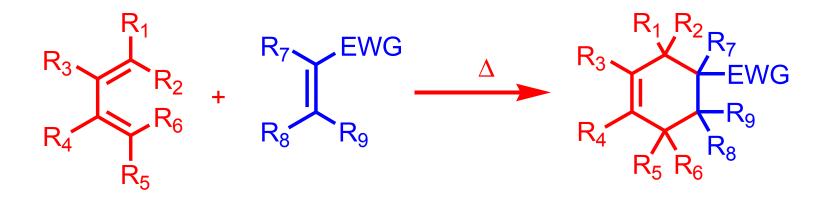


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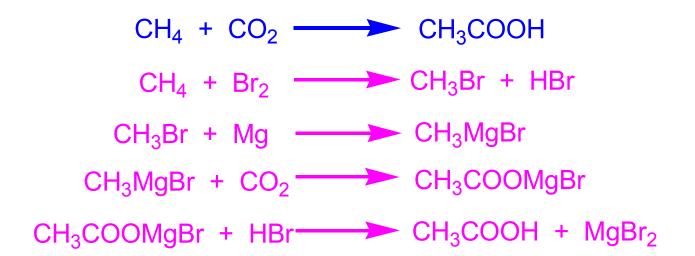


Nicolaou, K. C.; Sorensen, E. J. Classics in Total Synthesis, VCH, Weinheim, Germany, 1996.

Organic Reaction Vs Synthetic Method



General approach to the solution of organic synthesis problems





The Nobel Prize in Chemistry 2005

"for the development of the metathesis method in organic synthesis"



Yves Chauvin

 \bigcirc 1/3 of the prize



Robert H. Grubbs \bigcirc 1/3 of the prize

France Institut Français du Pétrole Rueil-Malmaison, France

USA California Institute of Technology (Caltech) Pasadena, CA, USA Cambridge, MA,



Richard R. Schrock

 \bigcirc 1/3 of the prize USA

Massachusetts Institute of Technology (MIT) USA

12/28/10

b. 1930

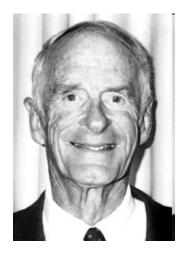
b. 1942

b. 1945



Nobel Prize in Chemistry 2001

one half to William S. Knowles and Ryoji Noyori *"for their work on chirally catalysed hydrogenation reactions"* **and** the other half to K. Barry Sharpless *"for his work on chirally catalysed oxidation reactions"*



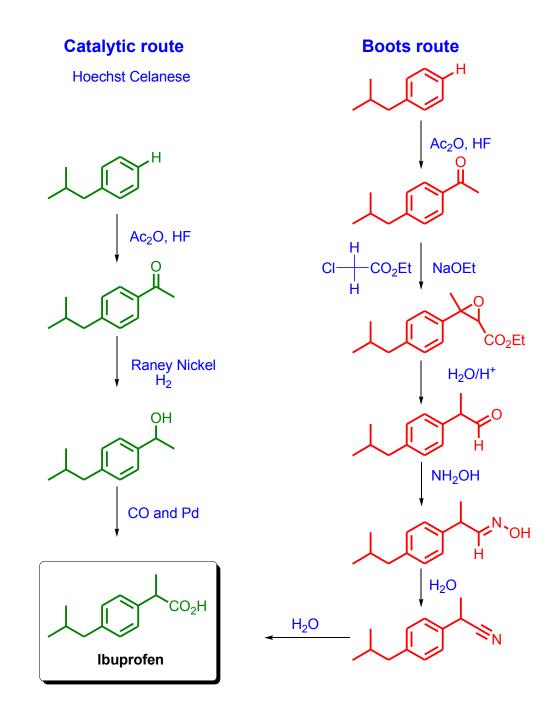
William S. Knowles



Ryoji Noyori



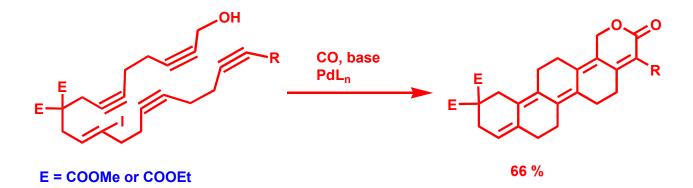
K. Barry Sharpless



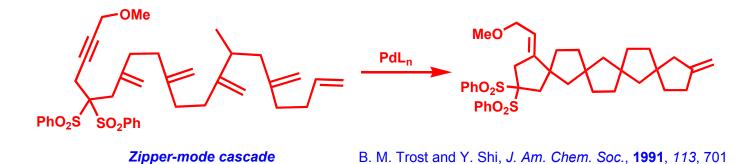
Commonly used Aryl-Aryl couplings methods

Ar—Br	+ Ar'—Br	Cu 🗲	Ar—Ar'	Ullmann Coupling
Ar-MgCl	+ Ar'—Br	Ni or Pd 🔶	Ar—Ar'	Kumada Coupling
Ar-ZnCl	+ Ar'—Br	Pd >	Ar—Ar'	Negishi Coupling
Ar—SnBu ₃	+ Ar'—Br	Pd >	Ar—Ar'	Stille Coupling
Ar B(OH) ₂	+ Ar'—Br	Pd >	Ar—Ar'	Suzuki Coupling
Ar—Si(R') ₃	+ Ar'—Br	Pd	Ar—Ar'	Hiyama Coupling

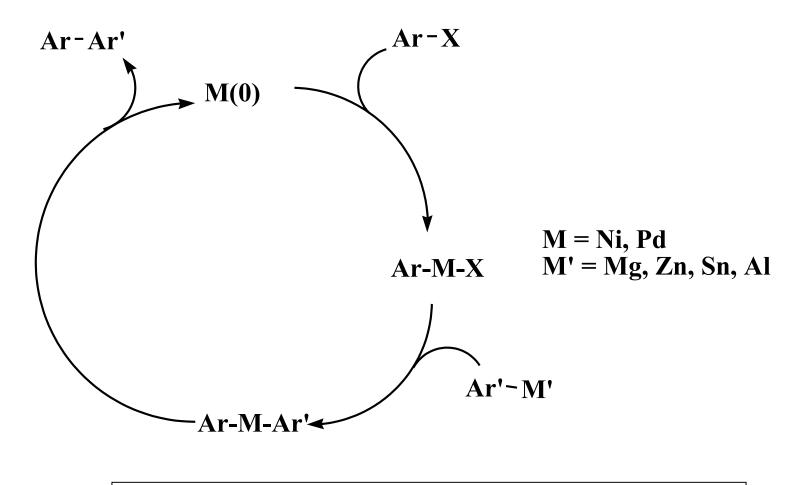
Zipper-mode cascade reaction with Pd



T. Sugihara, C. C. Coperet, Z. Owczarczyk, L. S. Harring, and E. Negishi, *J. Am. Chem. Soc.*, **1994**, *116*, 7923



Catalytic cycle for cross-coupling reaction

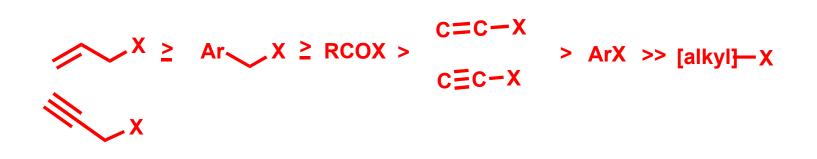


Martin, A. R.; Yang, Y. Acta. Chim. Scand. 1993, 47, 221

Relationship Between Some Fundamental Properties of Pd and Chemical Consequences

Fundamental Properties of Pd	Consequences
Moderately large size	 Moderate stability of organopalladiums (Ni<pd<pt)< li=""> </pd<pt)<>
 Strong preference for 0 and +2 oxidation states separately by a relatively narrow energy gap. 	 Relatively rare one-electron or radical process (e.g., relative to Ni). Ready and reversible two-electron oxidation and reduction.
12/28/10	(C ataly sis) 19

Functional Group Reactive Toward Pd



- 1. Alkyl halides lacking proximal π or n-donar groups are relatively inert but included for comparison.
- The X group and approximate reactive order are: I > OTf > Br >CI > OZ > NZ₂, CZ₃, etc., where Z is any atom or group attached to O, N, and C.
- 3. Electron-poor aryl or vinyl halides react with Pd(0) complexes faster than electron rich halides.

Electronegativity Values and Ionic Character

Element	Li	Mg	Ti	ΑΙ	Zn	Cu	
EN	0.97	1.23	1.32	1.47	1.66	1.75	
% Ionicity	43	35	30	22	15	12	

Element	Si	Sn	В	С
EN	1.74	1.72	2.01	2.50
% Ionicity	12	11	6	

What is Suzuki Coupling reaction?



X=I, Br, OTfz

- a) Miyaura, N.; Suzuki, A. JCS. Chem. Commun. 1979, 866
- b) Miyaura, N.; Yamada, K.; Suzuki, A. Tetrahedron Lett. 1979, 3437.
- c) Miyaura, N.; Yanagi, T.; Suzuki, A. Synth. Commun. 1981, 513.

Recent application of the Suzuki-Miyaura cross-coupling reaction in organic synthesis

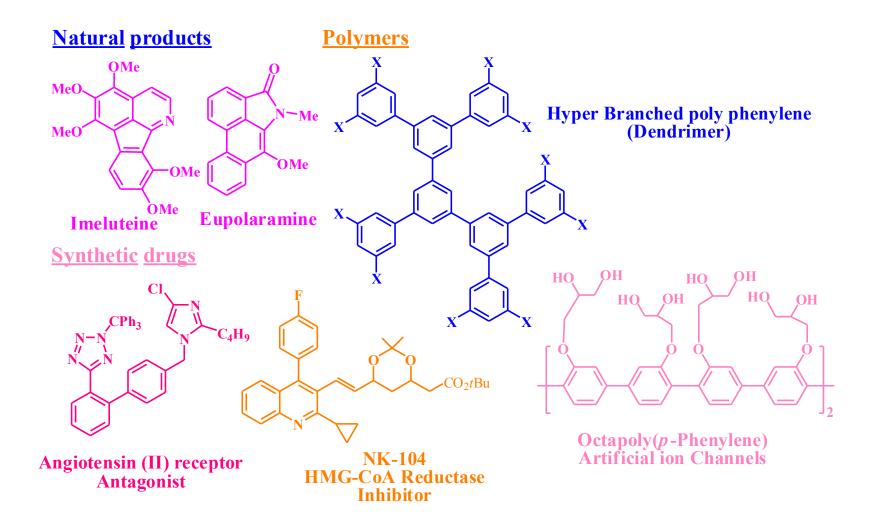
Kotha S.; Lahiri, K.; Kashinath, D. Tetrahedron 2002, 58, 9633.(750 citations)

Most requested documents-chemistry and related science CAS Science Spotlight 2003 & 2004 http://www.cas.org/spotlight

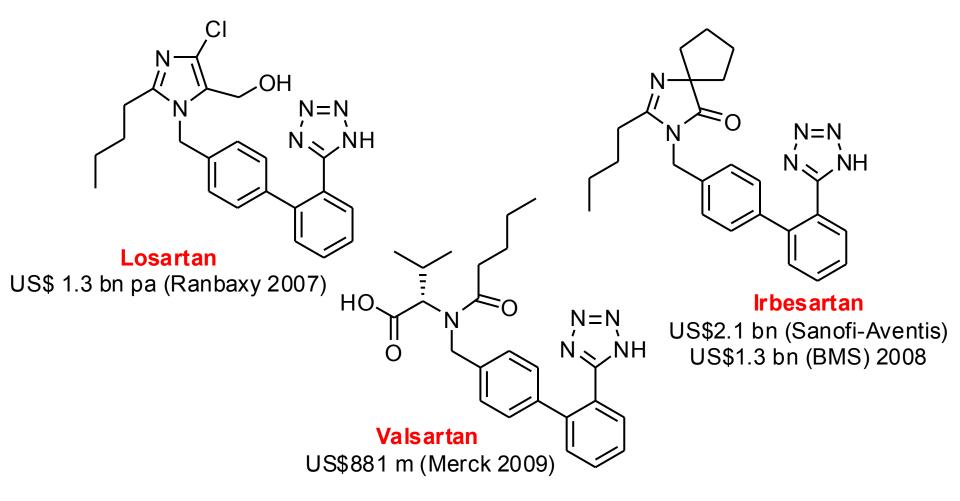
Best review paper award 2005 : I. I. T., Bombay

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Biologically important molecules with biaryl system



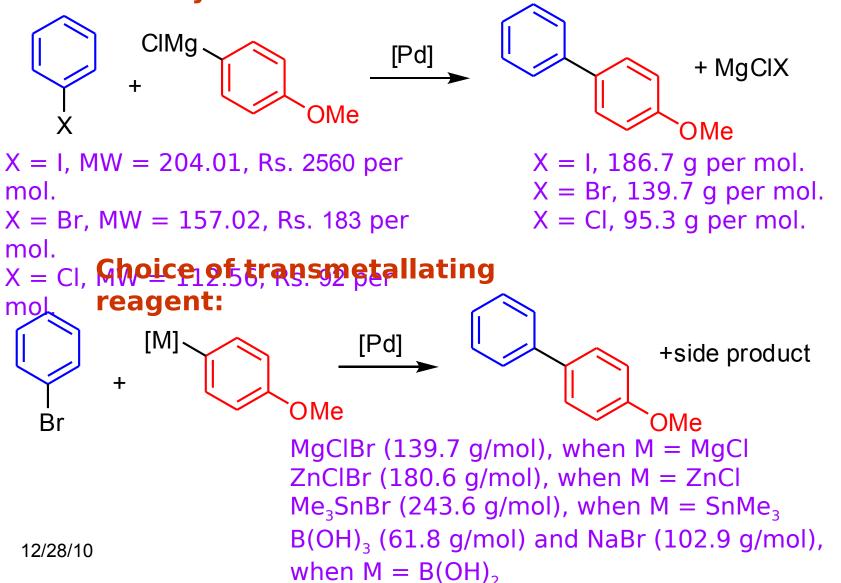
Application of biaryl compounds



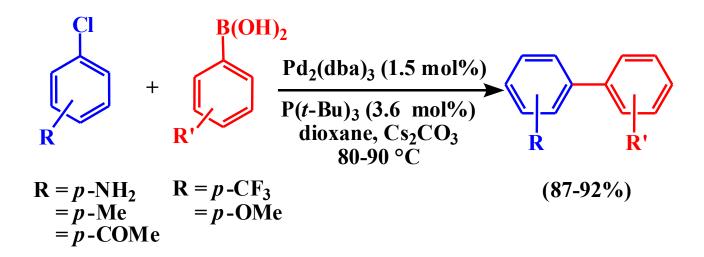
12/28/10 otensin II receptor antagonists (treatment of hypertension)

Reaction efficiency: atom-economy

Choice of aryl halide:

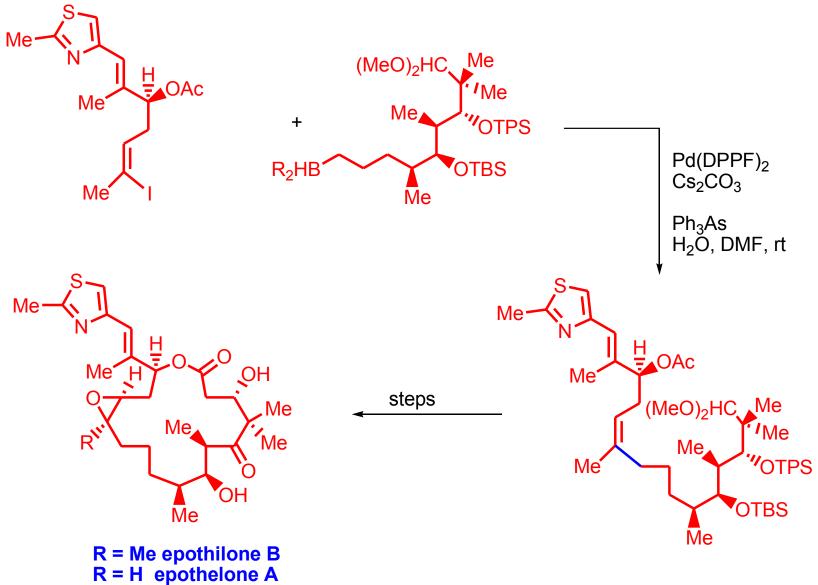


25

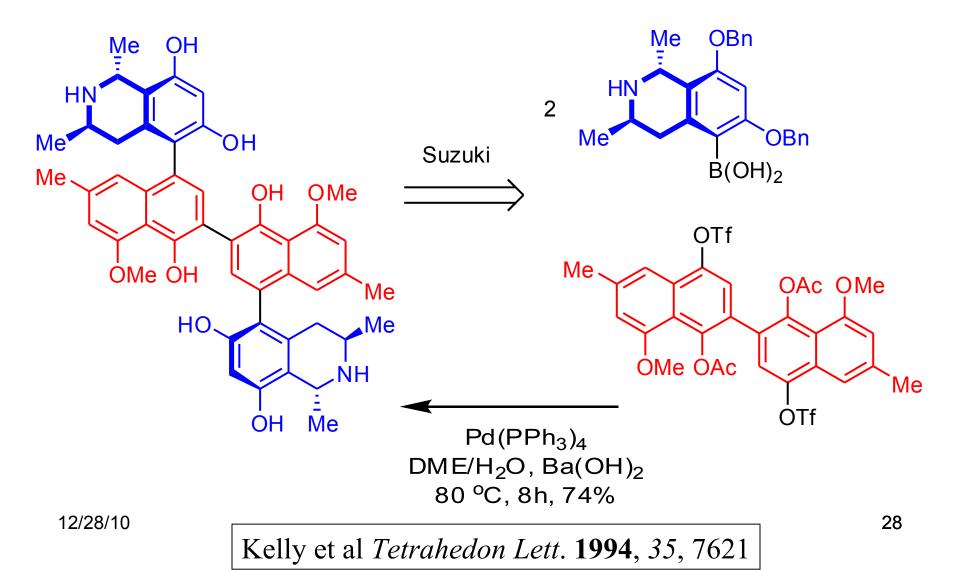


Littke et al Angew. Chem. Int. Ed. Eng. 1998, 38, 3387

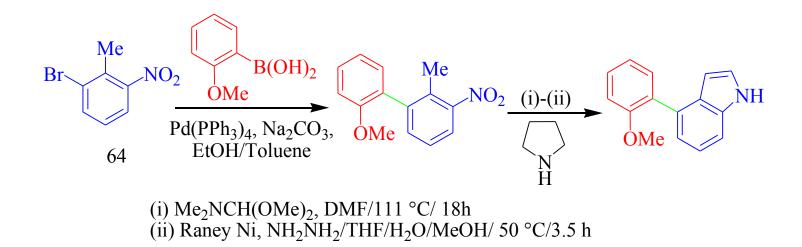
Synthesis of anticancer drugs



Total synthesis of Michellamine B:



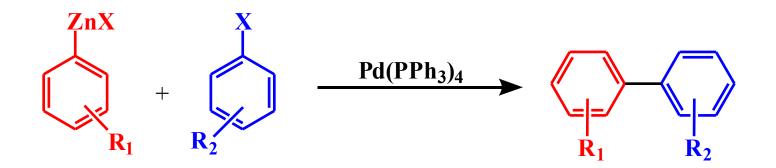
Synthesis of 4-arylindole-portion diazonamide



- A natural antitumor agent
- In 1999, Magnus et al reported synthesis of 4-arylindole portion of the antitumor agent using SM coupling reaction in 76% yield

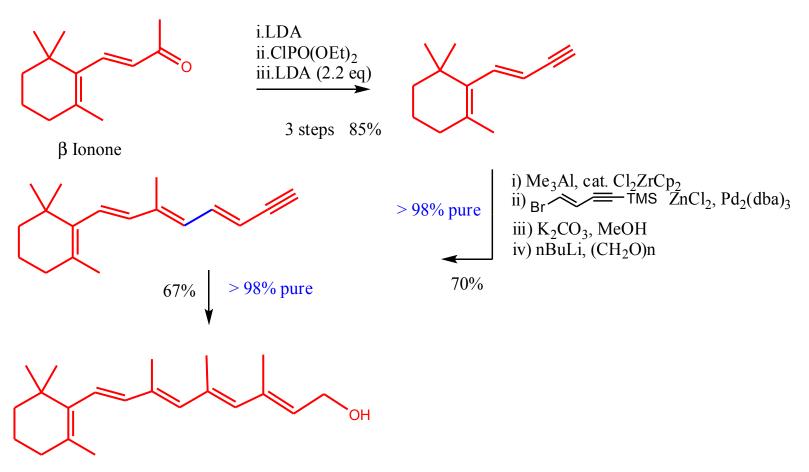
12/28/10 Chan, F.; Magnus, P.; McIver, G. E. *Tetrahedron Lettt.* 2000, *41*, 835

General representation of Negishi reaction

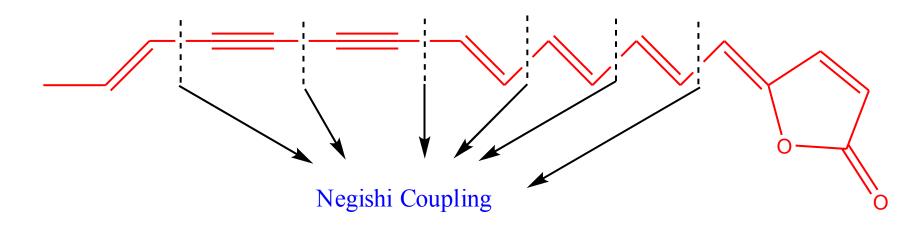


Roth et al. J. Org. Chem. 1991, 56, 3077.

Synthesis of Vitamin A

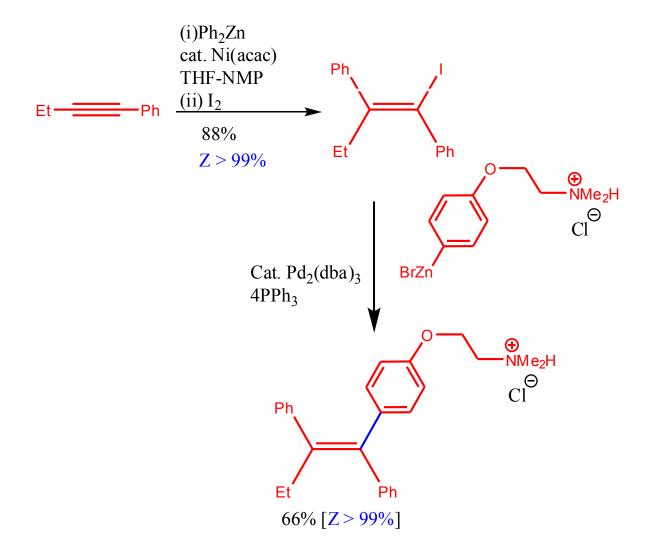


Vitamin A (> 98% pure)



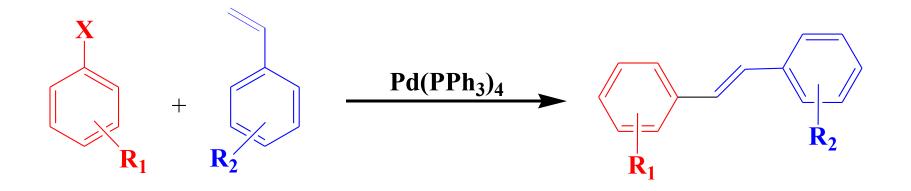
Xerulin: an inhibitor of cholesterol biosynthesis

Tamoxifen Hydrochloride: Drug to cure breast cancer



(Z) Tamoxifen Hydrochloride

General representation of Heck reaction

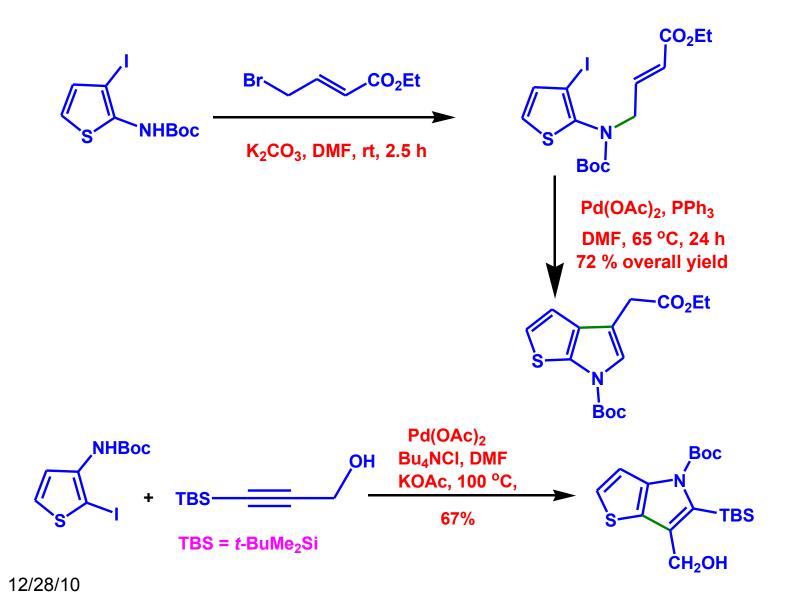


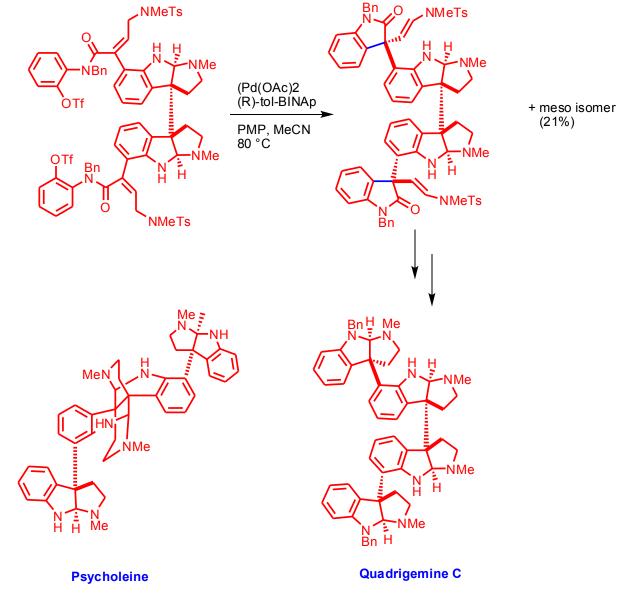
The greatest social impact of the Heck reaction has been its use in the coupling of alkynes to aryl halides; a reaction which was used to couple fluorescent dyes to DNA bases, allowing the automation of DNA sequencing and the elucidation of the human genome.

Name reactions for homologations Part-I Jie Jack Li. 2009, page No. 3.

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Heck coupling for the synthesis of pyrroles





antagonist of the SRIF (somatostatin) 12/28/10 receptor Antibacterial and Analgesic

Our research topics

Suzuki Coupling Tetrahedron 2002, 58, 9633 Eur. J. Org. Chem. 2007, 1221

Metathesis

Indian J. Chem. 2001,763 Synlett 2007, 2767 Chem. Soc. Rev. 2009, 2065

Suzuki-Metathesis

Chem. Asian J. 2009, 354

[2+2+2] Cycloaddition *Eur. J. Org. Chem. 2005, 4741*

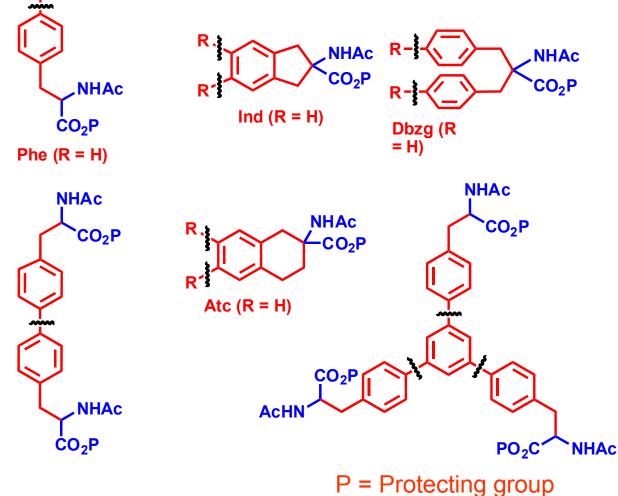
Rongalite Chem. Rev 2011, 000

Peptide Modifications Curr. Med. Chem. 2005, 12, 849

α-Amino Acids *Acc. Chem. Res.* 2003, 342 *Synlett.* 2010, 337

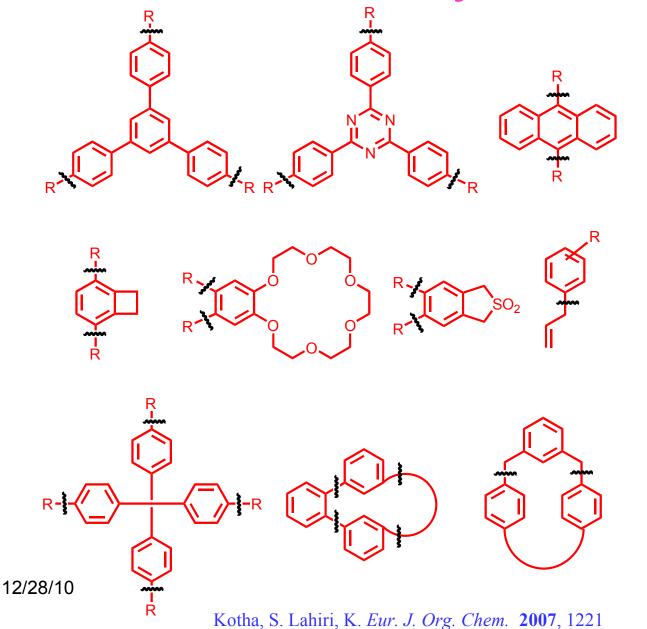
Polycyclics *Tetrahedron* 2001, *57*, 625 *Tetrahedron* 2008, *64*, 10775 *Synthesis* 2009, 165

Proposed list of constrained analogues of phenylalanine (Phe) for modification by SM



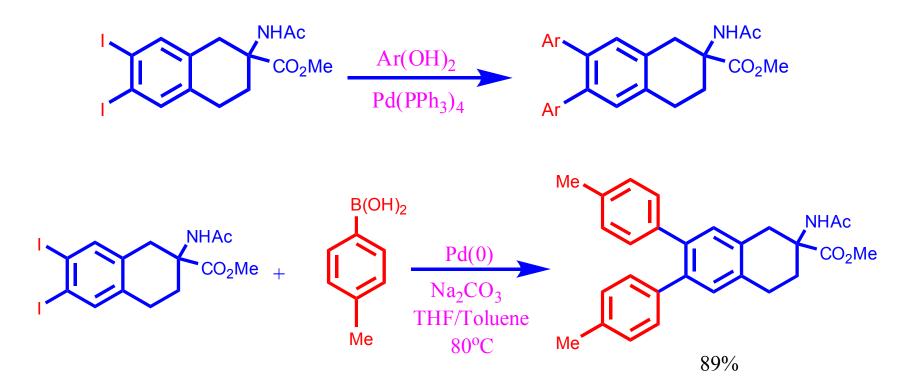
12/28/10 Kotha, S. Lahiri, K. Eur. J. Org. Chem. 2007, 1221

Several intricate molecular structures to demonstrate the utility of SM reaction



oling reactions from Kotha's (

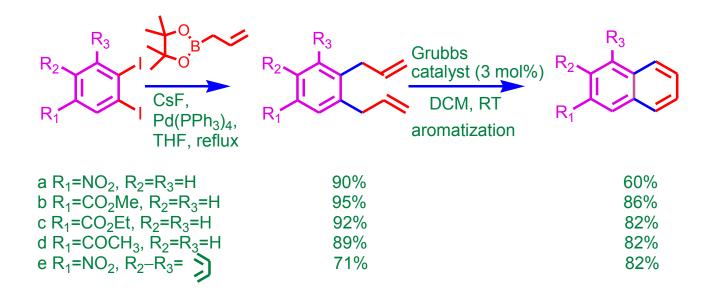
Tetralin-based amino acid derivatives by the Suzuki-Miyaura cross-coupling



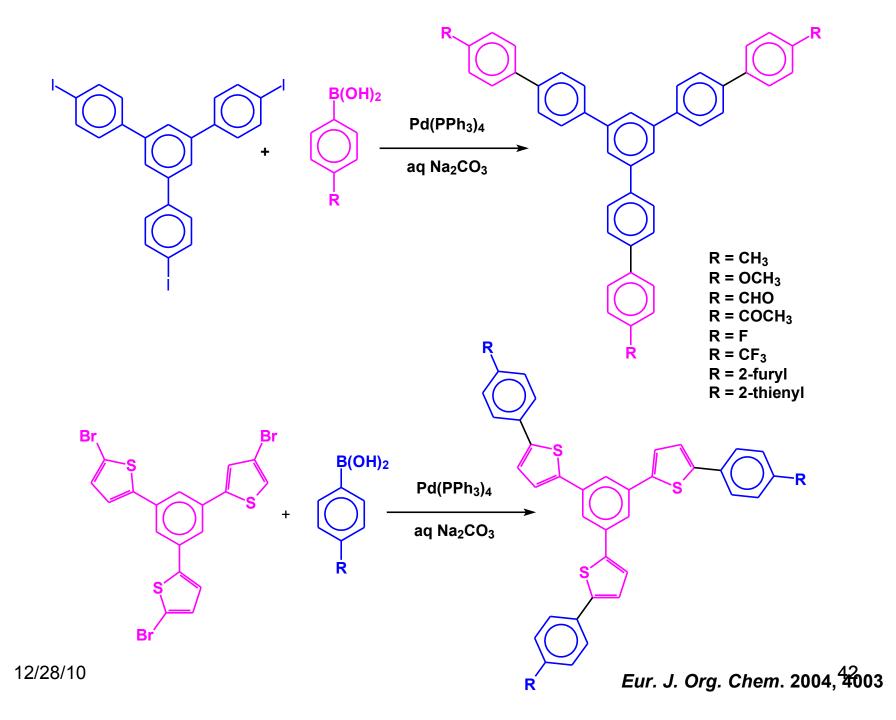
Kotha, S.; Ghosh, A. K. Synthesis 2004, 558.

12/28/10

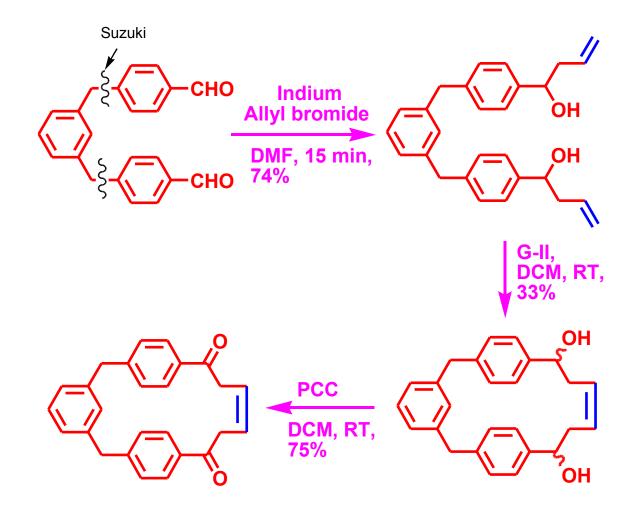
Suzuki Coupling and RCM method towards the synthesis of Benzoannulated products



Kotha, S.; Shah, V. R.; Mandal, K. *Adv. Synth. Catal.* **2007**, *349*, 1159-1172. 12/28/10



Synthesis of Cyclophanes

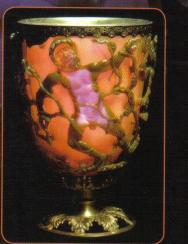


12/28/dtha, S.; Mandal, K.; Arora, K. K.; Pedireddi, V. R. Adv. Synth. Catal. 2005, 347, 1215. 43

Supramolecular Chemistry

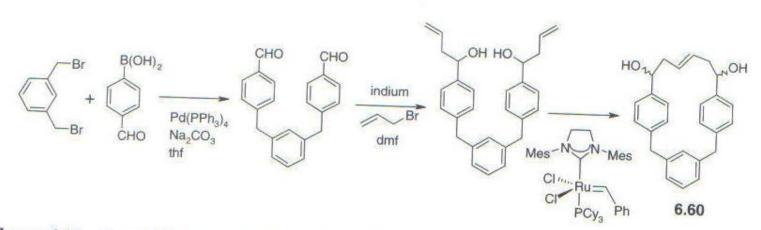
Jonathan W. Steed and Jerry L. Atwood

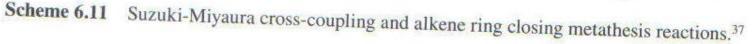
Second Edition





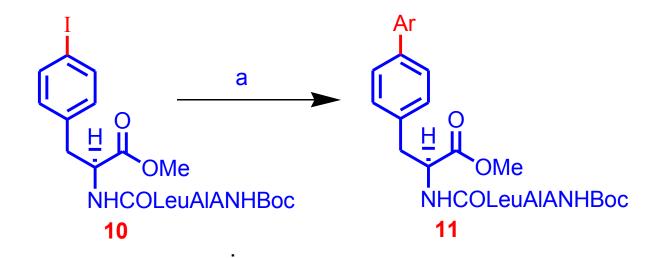






7. Alkene metathesis. The alkene metathesis reaction won the 2005 Nobel prize in chemistry for Grubbs, Schrock and Chauvin and has become tremendously widely used across all branches of synthetic chemistry including macrocycle synthesis. The reaction involves the metathesis (exchange) of the carbon atoms from one double bond with those of another, hence it is particularly useful for marcocyclisation by linking together two pendant alkene groups. In the example shown in Scheme 6.11 the alkenes are installed by palladium-catalysed Suzuki-Miyaura cross-coupling, followed by alkylation. The alkene ring-closing metathesis reaction is then used to cyclise the product to give cyclophane **6.60**.³⁷

Suzuki coupling in phenylalanine based peptides



Reagents and conditions: (a) ArB(OH)₂, Pd(PPh₃)₄, Na₂CO₃, THF/ toluene (1:1)

Kotha, S.; Lahiri, K. *Bioorg Med. Chem. Lett.* **2001,** *11,* 2887. Kotha, S.; Lahiri, K. Biopolymers **2003**, *69*, 517.

DOI: 10.1002/cctc.200900300

Suzuki–Miyaura Couplings on Proteins: A Simple and Ready-to-use Catalytic System in Water

Verena Böhrsch^[a, b] and Christian P. R. Hackenberger*^[a]

Among the first post-synthetically modified peptides via Suzuki reaction were achieved by the Kotha group for the combinatorial synthesis of biologically active peptide libraries.^[19-21] In addition, the Suzuki-coupling has proven to be effective in solid-phase peptide synthesis and for the heterogeneous modification of peptides.^[22-24] Another interesting appli-

ChemCatChem 2010, 2, 243-245.

J. Comb. Chem. 2008, 10, 44-51

Effectiveness of the Suzuki-Miyaura Cross-Coupling Reaction for Solid-Phase Peptide Modification

Ngoc-Duc Doan, Steve Bourgault, Myriam Létourneau, and Alain Fournier*

Laboratoire d'études moléculaires et phamacologiques des peptides (LEMPP), INRS–Institut Armand-Frappier, Université du Québec, 245 Boul. Hymus, Pointe-Claire, QC, Canada H9R 1G6

Solid-phase synthesis via the Suzuki reaction of biarylalanine derivative libraries was also described.¹⁵ The application of the SM cross-coupling reaction to 4-iodo-Lphenylalanine-based peptides was first investigated by Kotha and Lahiri,¹⁶ opening a new approach to produce unusual modified phenylalanine peptides. For example, dityrosine cross-linked peptide dimers were synthesized successfully.¹⁷

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Analyze Results

Rank the records by this field:	Analyze:	Set display options:	Sort by:
Country/Territory	Up to 100000 - Records.	Show the top 100	 Record count Selected field

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others)...

Note: The number of records displayed may be greater than the listed Record Count

View Records Exclude Records	Field: Institution Name	Record Count	% of 14790	Bar Chart	Save Analysis Data to File
	CALTECH	285	1.9270 %	1	
	CHINESE ACAD SCI	229	1.5483 <mark>%</mark>	1	
	MIT	222	1.5010 %	1	
	KYOTO UNIV	175	1.1832 %	1	
	INDIAN INST TECHNOL	170	1.1494 %	1	
	INDIAN INST CHEM TECHNOL	159	1.0751 %	1	
	MAX PLANCK INST KOHLENFORSCH	157	1.0615 %	1	
	UNIV FLORIDA	155	1.0480 %	1	
	CNRS	<mark>14</mark> 0	0.9466 %	1	
	RUSSIAN ACAD SCI	135	0.9128 %	1	
	TECH UNIV BERLIN	133	0.8993 %	1	
	TOHOKU UNIV	132	0.8925 %	1	
	UNIV WISCONSIN	132	0.8925 %	1	
	UNIV OXFORD	131	0.8857 %	1	

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Analyze Results

170 records. Topic=(metathesis)	=(metathesis)
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Analysis: Document Type=(ARTICLE OR REVIEW) AND Institutions=(INDIAN INST TECHNOL)

Rank the records by this field:	Analyze:	Set display options:	Sort by:
Authorsss Country/Territory Funding Agency Grant Number	Up to 500 - Records.	Show the top 100 - Results. Minimum record count (Threshold): 1	 Record count Selected field
Analyze		·	

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others)...

Note: The number of records displayed may be greater than the listed Record Count

View Records X Exclude Records	Field: Authorsss	Record Count	% of 170	Bar Chart	Save Analysis Data to File
	KOTHA, S	51	30.0000 %		
	KALIAPPAN, KP	<mark>1</mark> 9	11.1765 %		
	SUNDARARAJAN, G	15	8.8235 %		
	VANKAR, YD	13	7.6471 %		
	IQBAL, J	9	5.2941 %		
	MANDAL, K	8	4.7059 %		
	MOBIN, SM	8	4.7059 %		
	SREENIVASACHARY, N	8	4.7059 %		
	BRAHMACHARY, E	7	4.1176 %		
	SINGH, V	7	4.1176 %		
	HALDER, S	6	3.5294 %		
	LAHIRI, K	6	3.5294 %	1	
	ANAND, RC	5	2.9412 %		
	BANERJI, B	5	2.9412 %	1	

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5,235 records. Topic=(suzuki coupling) Analysis: Document Type=(ARTICLE OR REVIE)			
Rank the records by this field:	Analyze:	Set display options:	Sort by:
Funding Agency Grant Number Document Type Institution Name	Up to 100000 - Records.	Show the top 100 Results. Minimum record count (Threshold): 1	 Record count Selected field
Analyze			

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others)...

Note: The number of records displayed may be greater than the listed Record Count

View Records X Exclude Records	Field: Institution Name	Record Count	% of 5235	Bar Chart	Save Analysis Data to File
	CHINESE ACAD SCI	213	4.0688 %		
	INDIAN INST TECHNOL	65	1.2416 %	L	
	CNRS	62	1.1843 %	1	
	NATL UNIV SINGAPORE	62	1.1843 %	1	
	MIT	60	1.1461 %	1	
	S CHINA UNIV TECHNOL	57	1.0888 <mark>%</mark>	1	
	UNIV PENN	52	0.9933 %	1	
	KYOTO UNIV	48	0.9169 %	1	
	UNIV ROSTOCK	48	0.9169 %	1	
	UNIV TOKYO	48	0.9169 %	1	
	UNIV DURHAM	47	0.8978 %	i.	
	EGE UNIV	45	0.8596 %	1	
	ZHEJIANG UNIV	44	0.8405 %	1	
	INONU UNIV	41	0.7832 %	1	
	ZHENGZHOU UNIV	41	0 7832 %	1	

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Analyze Results

65 records. Topic=(suzuki coupling)

Analysis: Document Type=(ARTICLE OR REVIEW) AND Institutions=(INDIAN INST TECHNOL)

Rank the records by this field:	Analyze:	Set display options:	Sort by:
Authorsss Country/Territory Funding Agency Grant Number	Up to 500 - Records.	Show the top 100 Results. Minimum record count (Threshold): 1	 Record count Selected field

Use the checkboxes below to view the records. You can choose to view those selected records, or you can exclude them (and view the others).

Note: The number of records displayed may be greater than the listed Record Count

View Records	Field: Authorsss	Record Count	<mark>%</mark> of 65	Bar Chart	Save Analysis Data to File
	KOTHA, S	28	43.0769 %		1
	BALAKRISHNA, MS	10	15.3846 %		
	MAGUE, JT	8	12.3077 %		
	LAHIRI, K	7	10.7692 %		
	PUNJI, B	6	9.2308 %		
	RAO, MLN	6	9.2308 %		
	SHAH, VR	6	9.2308 %		
	SINGH, AK	6	9.2308 %		
	GHOSH, P	5	7.6923 %		
	JADHAV, DN	5	7.6923 %		
	GHOSH, AK	4	6.1538 %		
	HALDER, S	4	6.1538 %		
	MANDAL, K	4	6.1538 %		
	SHAIKH, MM	4	6.1538 %		
m	VENKATESH V	4	6 1538 %		

Subject: many thanks for sending me a copy of your paper
From: "Akira Suzuki" <asuzuki@eng.hokudai.ac.jp>
Date: Tue, March 18, 2003 1:59 am
To: srk@chem.iitb.ac.in

Dear Professor Kotha:

Thank you very much for sending me a copy of your review paper on Tetrahedron, which I have recently received through Kurashiki University of Science and Arts. At the end of March in 2002, I retired from the University, and returned to my home in Hokkaido. Of course I read the review article before. It is actually very fine. I am very much pleased to learn that you and your group are interested in our coupling reaction.

Recently I have published a book, "Suzuki Coupling" from Aldrich early this year. I submitted the manuscript almost two years ago, but it took long time to be published. As I recognized that many chemists all over the world are interested in the reaction, I have decided to write the second book "Suzuki Coupling Part-2" and already started to write the manuscripts. So I hope you could have chance to read these books in near future.

Best regards,

Akira Suzuki



OFFICE OF THE PRESIDENT

Kita 8, Nishi 5, Kita-ku Sapporo, 060-0808 Japan Tel: +81-11-706-2334 Fax: +81-11-706-2095

December 15, 2004

Dear Sir or Madam:

I hope this letter finds you in excellent health and good spirits.

I am delighted to send you the collected research works of Dr. Akira SUZUKI, a Hokkaido University Professor Emeritus who has been presented with a Japan Academy Award.

He reported on the Palladium Catalyzed Cross Coupling Reactions of Organoboron Compounds in 1979 and exercised considerable influence over many fields, not only in synthetic organic chemistry but also in catalytic chemistry, material science and so forth. Via this research, he developed a new field of study, "Suzuki Coupling Reaction," which has gained worldwide recognition, and for which the award was conferred.

We made this collection of his research works to honor him and I should be very grateful if you would have a look at it.

Sincerely yours,

NAKAMURA Mutsuo

President Hokkaido University

Ph. D students

1. Dr. E. Brahmachary 2. Dr. N. S. Chary **3. Dr. R. Sivakumar** 4. Dr. E. Manivannan 5. Dr. S. Halder 6. Dr. (Ms). K. Lahiri 7. Dr. K. Mohanraja 8. Dr. M. Behera 9. Dr. A. Ghosh 10. Dr. A. C. Deb 11. Dr. D. Kasinath 12. Dr. K. Mandal 13. Dr. S. Banerjee 14. Dr. K. Singh 15. Dr. V. Shah 16. Dr. (Ms). P. Khedkar 17. Dr. M. K. Dipak 18. Ms. A. Tiwari 19. Ms. N. G. Krishanan 20. Mr. S. Vittal **21. Ms. S. Misra** 22. Mr. A. S. Chavan

23. Ms. D. Bansal
24. Mr. M. P. Meshram
25. Mr. G. Waghule
26. Mr. M. Shirbhate
27. Mr. R. Ali

Post-doctoral students

Dr. T. Ganesh
 Dr. R. Vinod. Kumar
 Dr. S. Kumar
 Dr. (Ms). K. Lahiri
 Dr. D. Nagaraju
 Dr. (Ms). P. Khedkar
 Dr. T. Niranjan

Project/Summer students

- 1. Mr. S. M. Husian
- 2. Mr. M. J. Rihan
- 3. Ms. M. Sridevi
- 4. Mr. A. Pradeesh
- 5. Ms. B. V. Lakshmi

M. Sc. students

1. Mr. S. A. Jothi

- 2. Mr. G. Giridharan
- 3. Ms. R. Deshpande
- 4. Ms. M. S. Subhashi
- 5. Mr. S. R. Subbaiah
- 6. Mr. A. Mehta
- 7. Mr. C. Chatterjee
- 8. Mr. AP. Suresh Babu
- 9. Ms. S. Bhattacharjee
- **10. Mr. P. Charkrabarty**
- 11. Mr. T. Kesharwani
- 12. Mr. A. Singh
- 13. Mr. V. Rane
- 14. Mr. A. Pal
- 15. Mr. T.T. Rao
- 16. Mr. M. Banik
- 17. Mr. R. K. Das
- 18. Mr. V. Shukla
- 19. Mr. U. Basu
- 20. Mr. K. Raju
- 21. Ms. G. Rama



Thank You