Green Chemistry Innovation in the Synthesis of Medicines

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http://www.drreddys.com/products/green-chemistry.html (Green Chemistry Website)

Nature Medicine **2013**, *19*, 1200-1203 (Finding Right Chemistry)

Significance of Chemistry

•Whatever you hear, see, smell, taste, and touch involves chemistry and chemicals (matter).

•And all these processes involve intricate series of chemical reactions and interactions in the biological system.

• With such an enormous range of biological actions which are governed by chemistry therefore it is essential to know about this subject at some level in order to understand the world around us.

Green Tea 

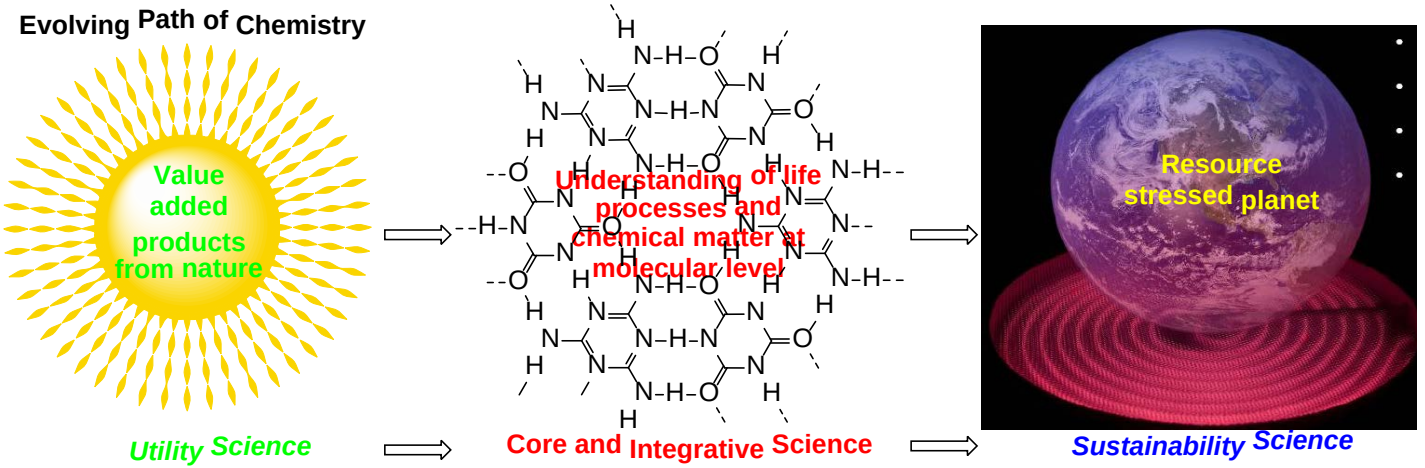
>200

Coffee 

>1000 Chemicals

Cigarette 

>7000



Significance of Chemistry

-To quote Linus Pauling, Nobel Laureate in chemistry, from a 1983 UC Berkeley lecture:

Chemistry is wonderful! I feel sorry for people who don't know anything about chemistry. They are missing an important source of happiness -- that of satisfying one's intellectual curiosity. The world is wonderful. Chemistry is an important part of it.

Chemistry Signifies Love and Hate Relationship

-can't live without it but can't accept everything that it has

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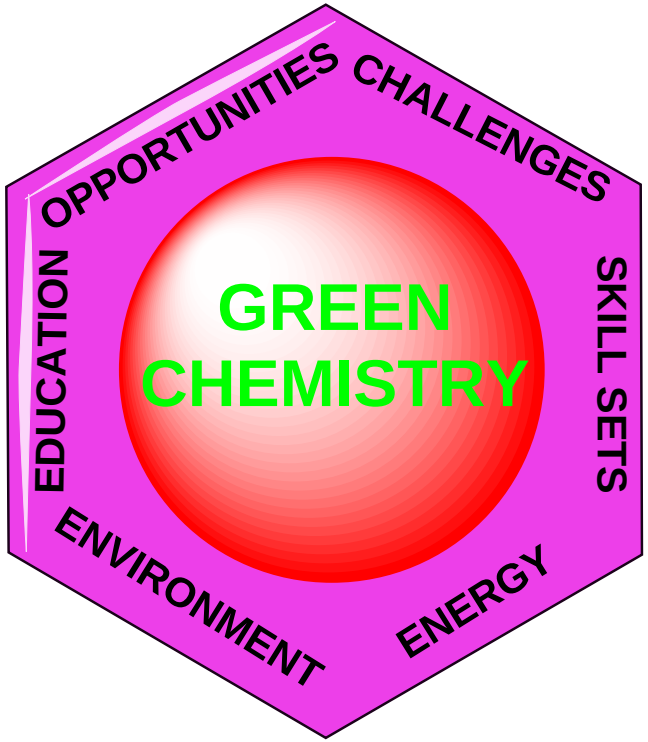
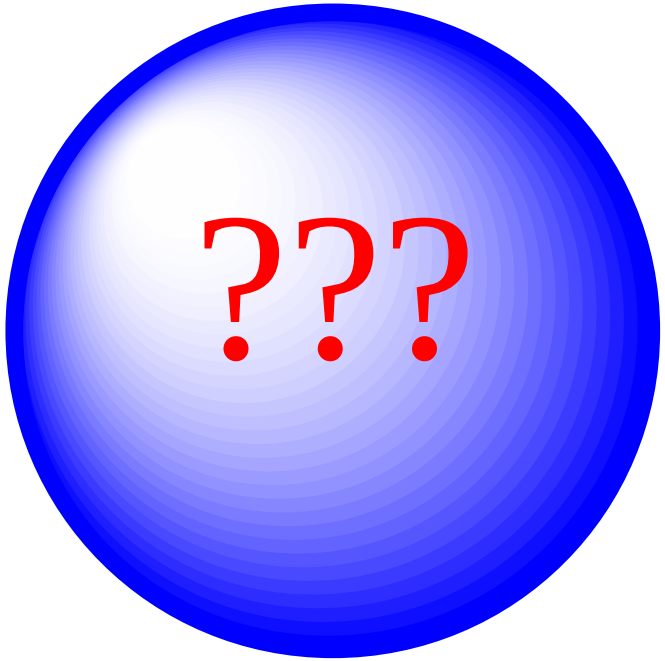
•Evolving discipline it does mean that the definition of green may change tomorrow e.g. Grignard reaction was considered to be one of the best reactions but today it is being replaced with greener metal catalyzed transformations.

•It is a subject that deals with prevention of waste in any activity around us by design.





Industry Sectors

Energy alternatives

Textile, printing, agro and construction

Electronics and semiconductors

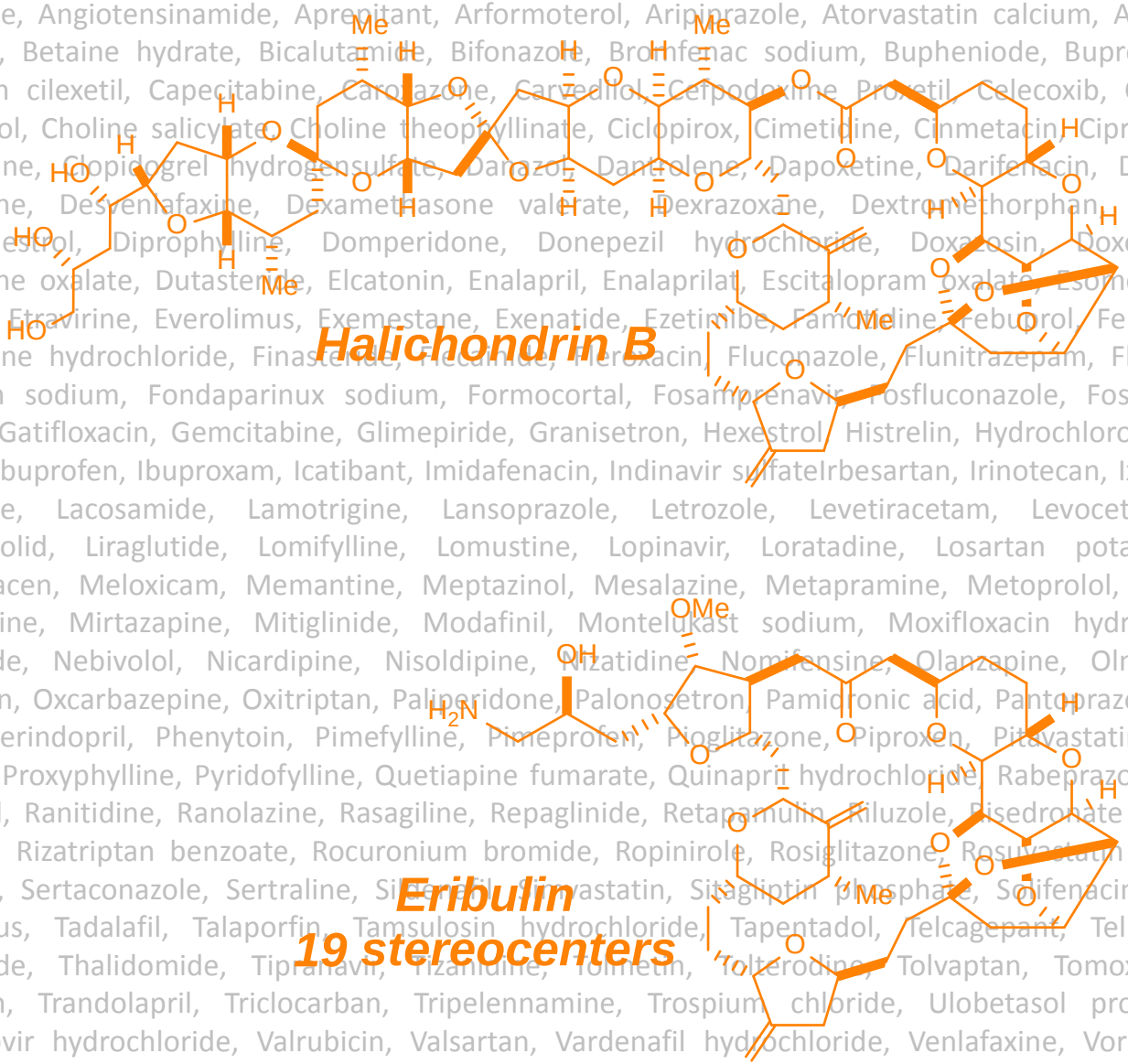
Pharmaceutical, medical and biotech

Cosmetics

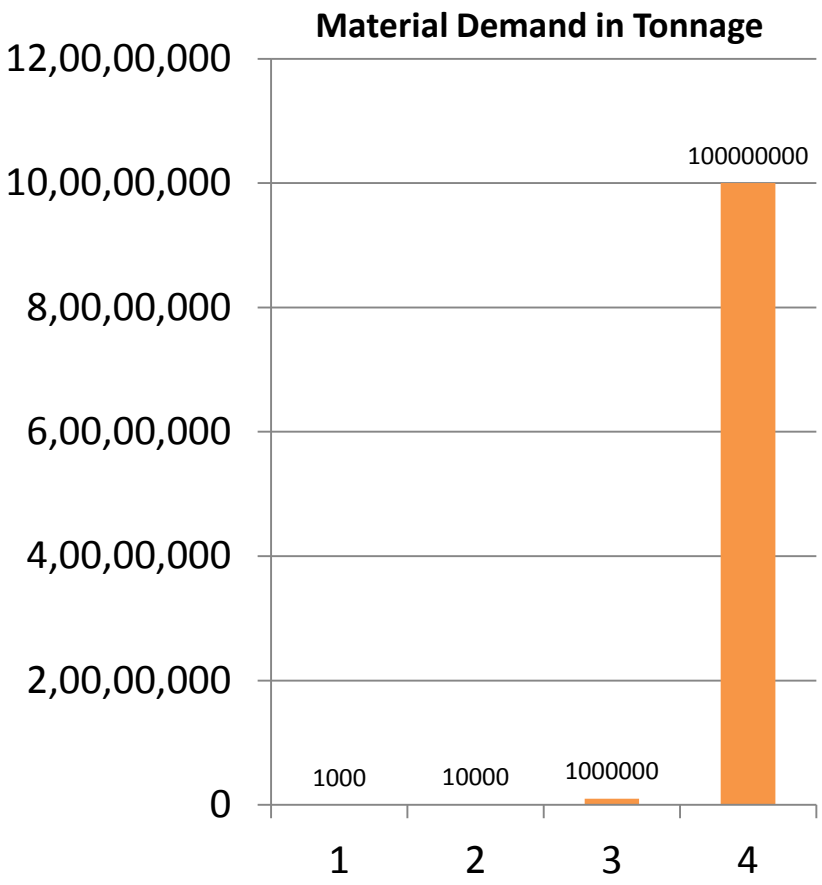
Retail and everyday commodity

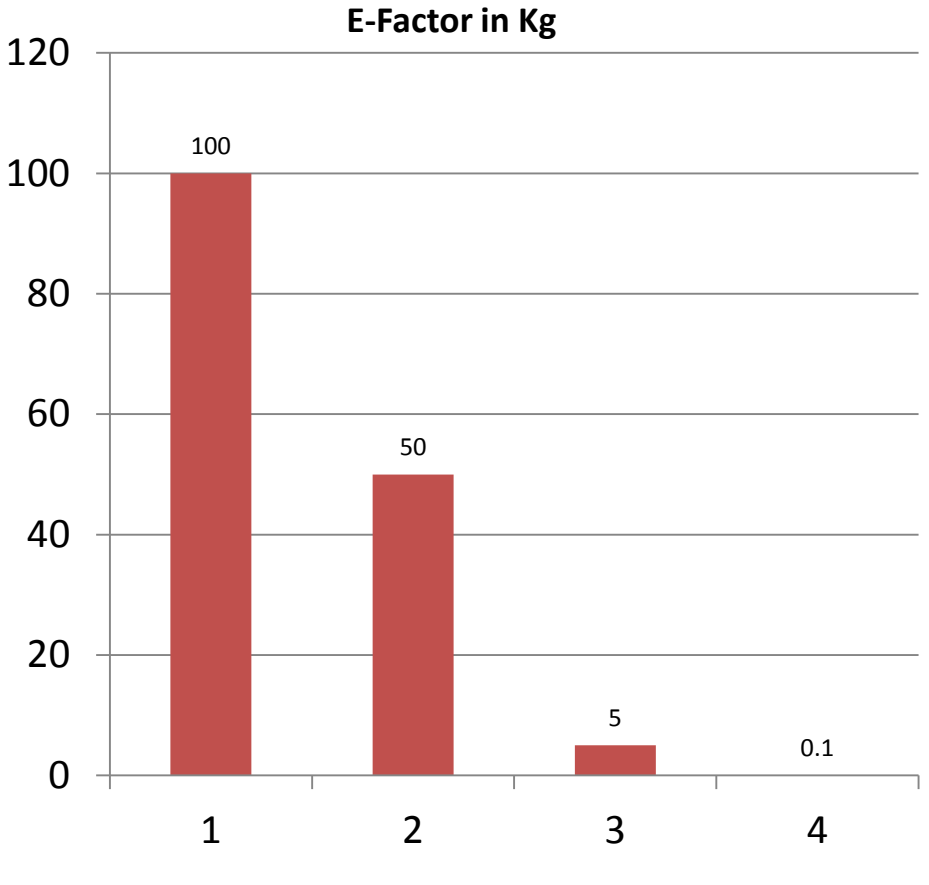
Complexity

Abacavir, Acefylline, Acrivastine, Alendronate sodium, Alfuzosin, Almotriptan, Altretamine, Alvimopan, Amifostine, Amlodipine, Amprenavir, Anastrozole, Angiotensinamide, Aprepitant, Arformoterol, Aripiprazole, Atorvastatin calcium, Azacitidine, Azelastine, Bamifylline, Benazepril, Betaine hydrate, Bicalutamide, Bifonazole, Brompheniramine sodium, Bupheniode, Buprenorphine, Cafedrine, Calcitonin, Candesartan cilexetil, Capecitabine, Carfilzomib, Carvedilol, Cefpodoxime Proxetil, Celecoxib, Cetalkonium chloride, Cetirizine, Chlorobutanol, Choline salicylate, Choline theophyllinate, Ciclopirox, Cimetidine, Cinmetacin, Ciprofloxacin, Citalopram, Clomifene, Clomipramine, Clopidogrel hydrogensulfate, Darunavir, Dantrolene, Dapoxetine, Darifenacin, Darunavir, Decitabine, Degarelix, Desloratadine, Desvenlafaxine, Dexamethasone valerate, Dexrazoxane, Dextromethorphan, Dezocine, Diazepam, Diethylstilbestrol, Dimestrol, Diprophylline, Domperidone, Donepezil hydrochloride, Doxazosin, Doxofylline, Doxylamine, Dronedarone, Duloxetine oxalate, Dutasteride, Elcatonin, Enalapril, Enalaprilat, Escitalopram oxalate, Esomeprazole, Eszopiclone, Ethinamate, Etofylline, Etravirine, Everolimus, Exemestane, Exenatide, Ezetimibe, Famotidine, Feburtol, Felodipine, Fenclofenac, Fenetylline, Fexofenadine hydrochloride, Finasteride, Flecainide, Floxacin, Fluconazole, Flunitrazepam, Fluoxetine, Fluticasone propionate, Fluvastatin sodium, Fondaparinux sodium, Formocortal, Fosamprenavir, Fosfluconazole, Fosinopril, Fosphenytoin sodium, Galantamine, Gatifloxacin, Gemcitabine, Glimepiride, Granisetron, Hexestrol, Histrelin, Hydrochlorothiazide, Ibandronate sodium monohydrate, Ibuprofen, Ibuproxam, Icatibant, Imidafenacin, Indinavir sulfate, Irbesartan, Irinotecan, Ixabepilone, Ketorolac, Lacidipine, Lacosamide, Lacosamide, Lamotrigine, Lansoprazole, Letrozole, Levetiracetam, Levocetirizine, Levofloxacin, Levosalbutamol, Linezolid, Liraglutide, Lomifylline, Lomustine, Lopinavir, Loratadine, Losartan potassium, Mabuprofen, Meclofenoxate, Melitracen, Meloxicam, Memantine, Meptazinol, Mesalazine, Metapramine, Metoprolol, Miglitol, Milnacipran hydrochloride, Minaprine, Mirtazapine, Mitiglinide, Modafinil, Montelukast sodium, Moxifloxacin hydrochloride, Naproxen, Naratriptan, Nateglinide, Nebivolol, Nicardipine, Nisoldipine, Nizatidine, Nomifensine, Olanzapine, Olmesartan medoxomil, Ondansetron, Oxaprozin, Oxcarbazepine, Oxitriptan, Paliperidone, Palonosetron, Pamidronic acid, Pantoprazole sodium, Parecoxib sodium, Paroxetine, Perindopril, Phenytoin, Pimefylline, Pimeprofen, Pioglitazone, Piroxen, Pitavastatin, Prednival acetate, Pregabalin, Primidone, Proxyphylline, Pyridofylline, Quetiapine fumarate, Quinapril hydrochloride, Rabeprazole sodium, Raloxifene hydrochloride, Ramipril, Ranitidine, Ranolazine, Rasagiline, Repaglinide, Retapamulin, Riluzole, Risedronate sodium, Risperidone, Ritonavir, Rivastigmine, Rizatriptan benzoate, Rocuronium bromide, Ropinirole, Rosiglitazone, Rosuvastatin calcium, Rupatadine, Salmeterol, Saxagliptin, Sertaconazole, Sertraline, Sildenafil, Simvastatin, Sitagliptin phosphate, Solifenacin, Sulindac, Sulpiride, Sumatriptan, Tacrolimus, Tadalafil, Talaporfin, Tamsulosin hydrochloride, Tapentadol, Telcagepant, Telmisartan, Tenoxicam, Terbinafine, Teriparatide, Thalidomide, Tipranavir, Tizanidine, Tolmetin, Tolterodine, Tolvaptan, Tomoxetine hydrochloride, Topiramate, Topotecan, Trandolapril, Triclocarban, Tripelennamine, Trospium chloride, Ulobetasol propionate, Valaciclovir, Valdecoxib, Valganciclovir hydrochloride, Valrubicin, Valsartan, Vardenafil hydrochloride, Venlafaxine, Voriconazole, Zafirlukast, Zalcitabine, Zaleplon, Ziprasidone hydrochloride, Zoledronic acid, Zolmitriptan, Zolpidem, Zonisamide



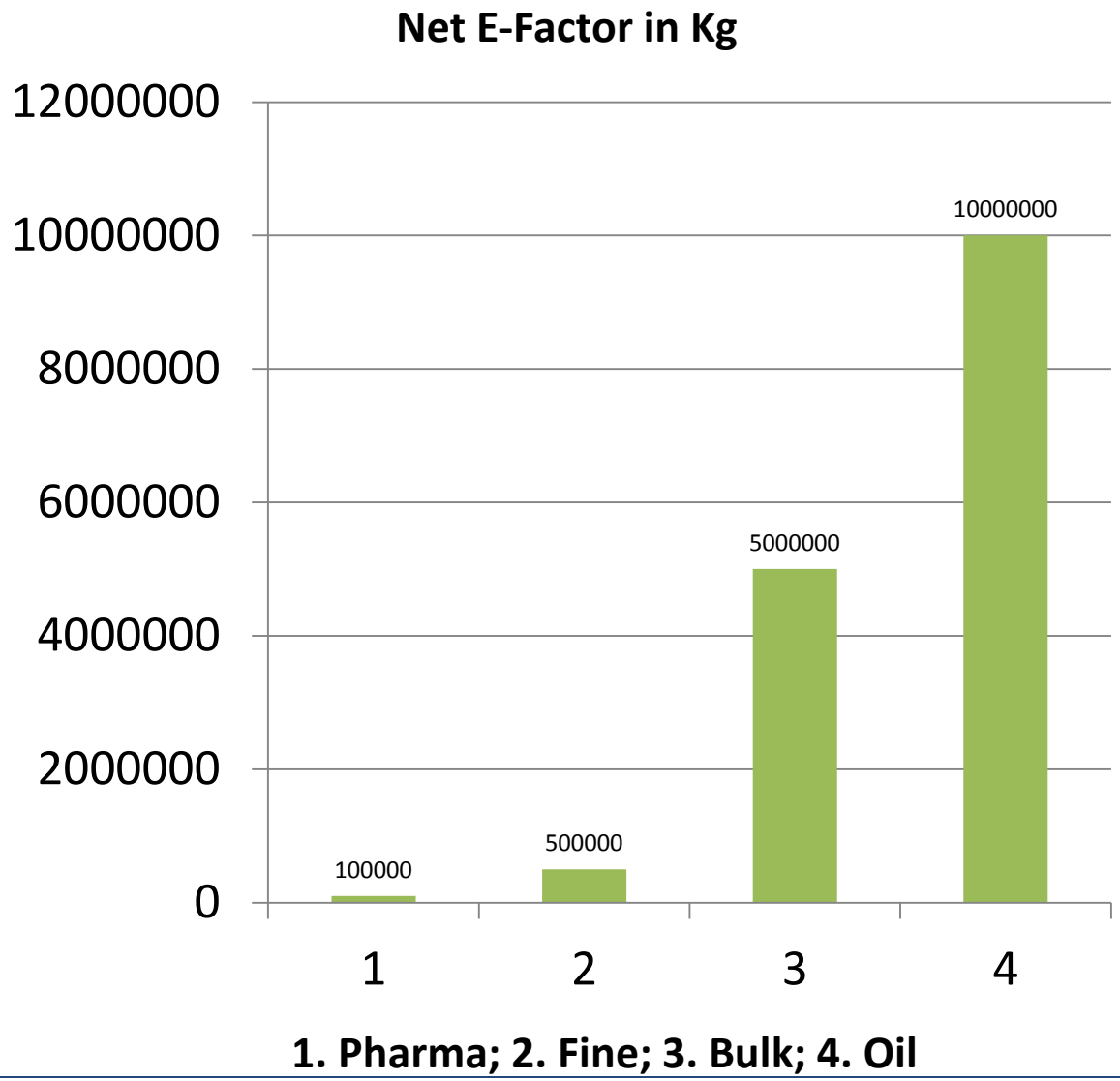
Higher E Factor α Degree of Complexity ?





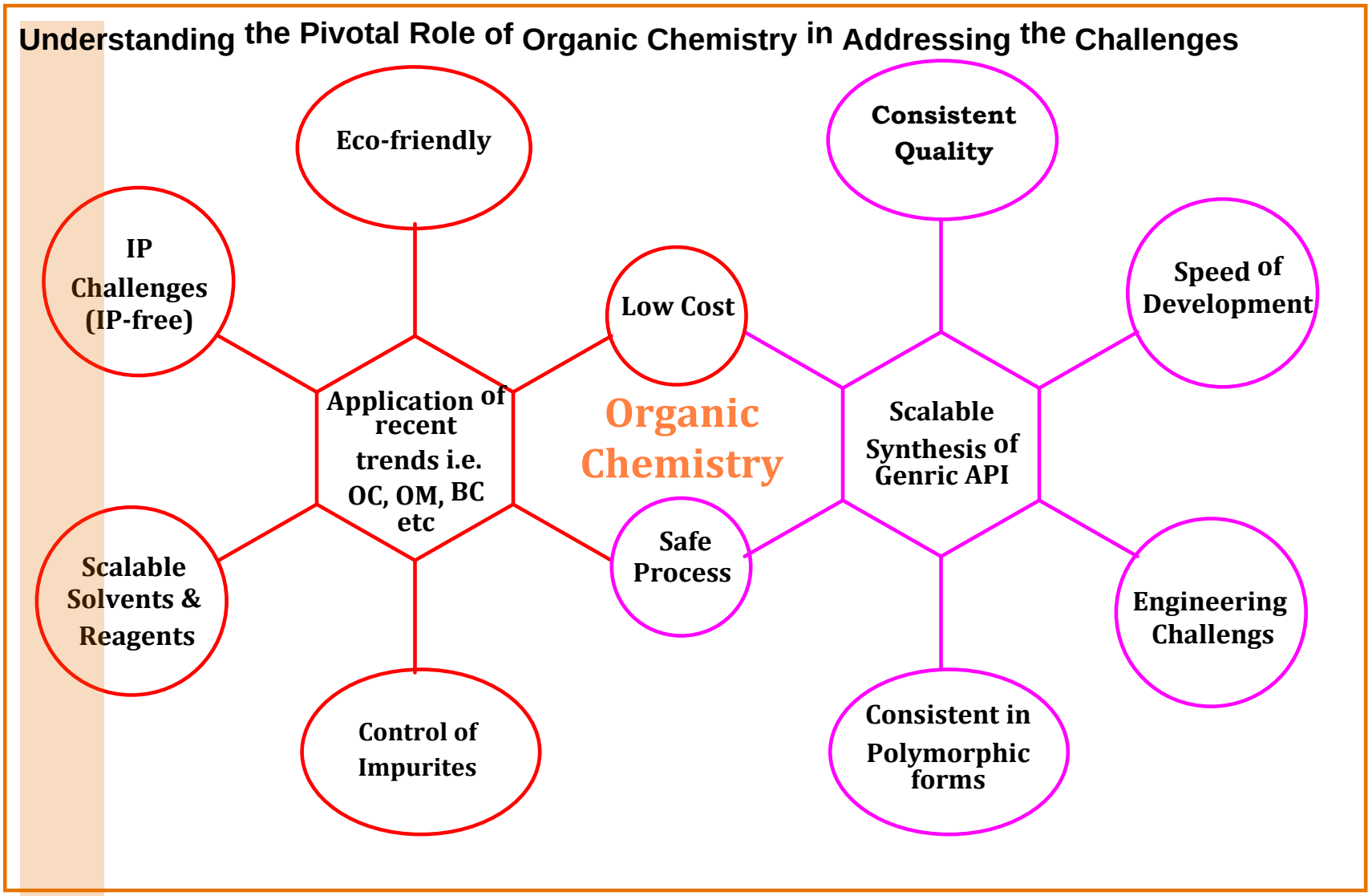
1. Pharma; 2. Fine; 3. Bulk; 4. Oil

Net E-Factor



1. Pharma; 2. Fine; 3. Bulk; 4. Oil

Approaches

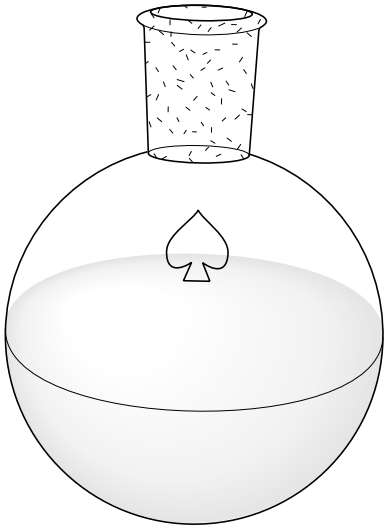

Understanding the Pivotal Role of Organic Chemistry in Addressing the Challenges
Eco-friendly
IP Challenges (IP-free)
Application of recent trends i.e. OC, OM, BC etc
Scalable Solvents & Reagents
Control of Impurites
Low Cost
Organic Chemistry
Safe Process
Consistent Quality
Speed of Development
Scalable Synthesis of Genric API
Engineering Challengs
Consistent in Polymorphic forms

Approaches

1. Consideration of GC (TP and GM) in design phase
2. Minimize the number of steps while maintaining the desired cost component intact
3. Minimize or replace (Switch) non-green solvents
4. Work through multi-disciplinary scientific interface (Collaboration)
5. Renewable material based synthesis
6. Net output based energy efficient waste (unavoidable) management
7. Non-toxic and hazard free practices
8. Continuous mode of Chemistry/Engineering (flow technology)
9. In-expensive catalyst based transformations
10. Opt for asymmetric transformations
11. Use of immobilized recombinant enzymes for transformations with very low dilutions
12. Educate and prepare young generation considering intuitive knowledge potential to take a lead in this field

Approaches: Flow Technology

BATCH
(space-resolved process)



- **Conventional method**
- **Several Disadvantages**
  - **Time and labor intensive**
  - **A number of unit processes**
  - **Needs extensive optimization**

FLOW MICROREACTION TECHNOLOGY
(time-resolved process)

- **Emerging Technology**
- **Advantages over batch process**
  - **High surface area, precisely controlled conditions**
  - **Rapid screening of reaction conditions**
  - **“Scale-out” instead of “Scale-up”**
  - **Safety**

Approaches: Biocatalysis

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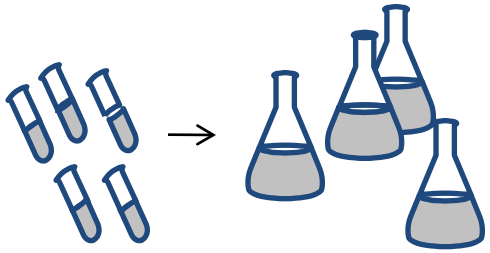
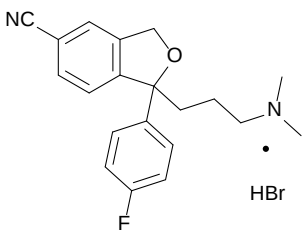
Screening → **Optimization** → **CPP** → **Production**



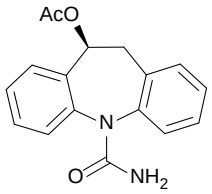
Microbe, enzyme collection | **Shake Flask** | **Lab Fermenter** | **Seed Fermenter** | **Production Fermenter**

Innovative Research Since 2007



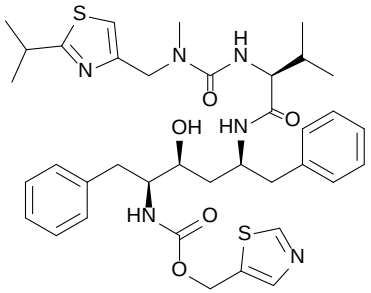
Citalopram

Org.Proc.Res.&Dev. **2013**, *17*, 798-805



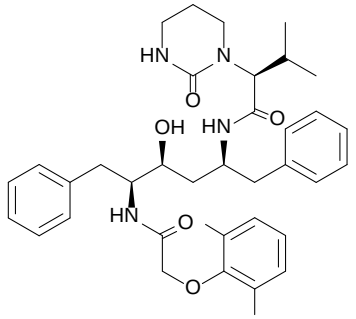
Esclicarzepine

Catal. Sci. Technol., **2012**, *2*, 1602-1605

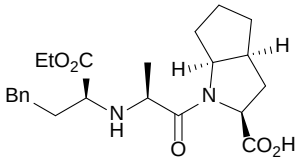


Ritonavir

Tetrahedron Lett. **2011**, *52*, 6968-6970

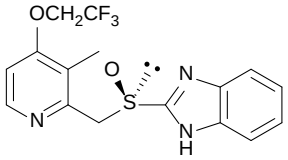


Lopinavir



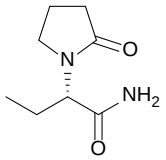
Ramipril

Synthetic Commun. **2011**, *41*, 1186-1191



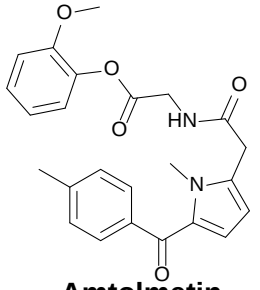
Dexlansoprazole

Tetrahedron Lett., **2011**, *52*, 5464-5468



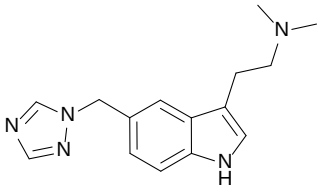
Levetiracetam

Green Chem. Lett. Rev. **2010**, *3*, 225-230



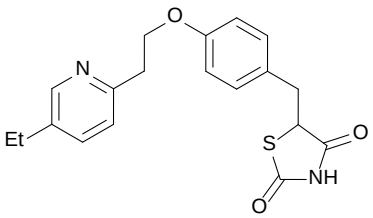
Amtolmetin

Org.Proc.Res.&Dev., **2010**, *40*, 362-368



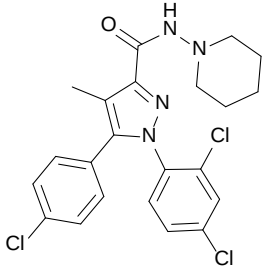
Rizatriptan

Org.Proc.Res.&Dev. **2009**, *13*, 683-689



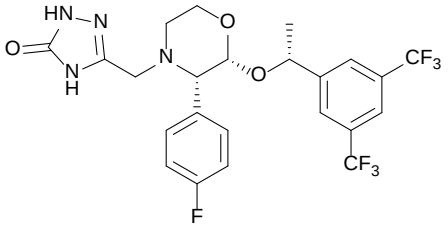
Pioglitazone

Org.Proc.Res.&Dev., **2009**, *13*, 1190-1194



Rimonabant

Monatsh. Chem., **2008**, *139*, 1091-1094



Aprepitant

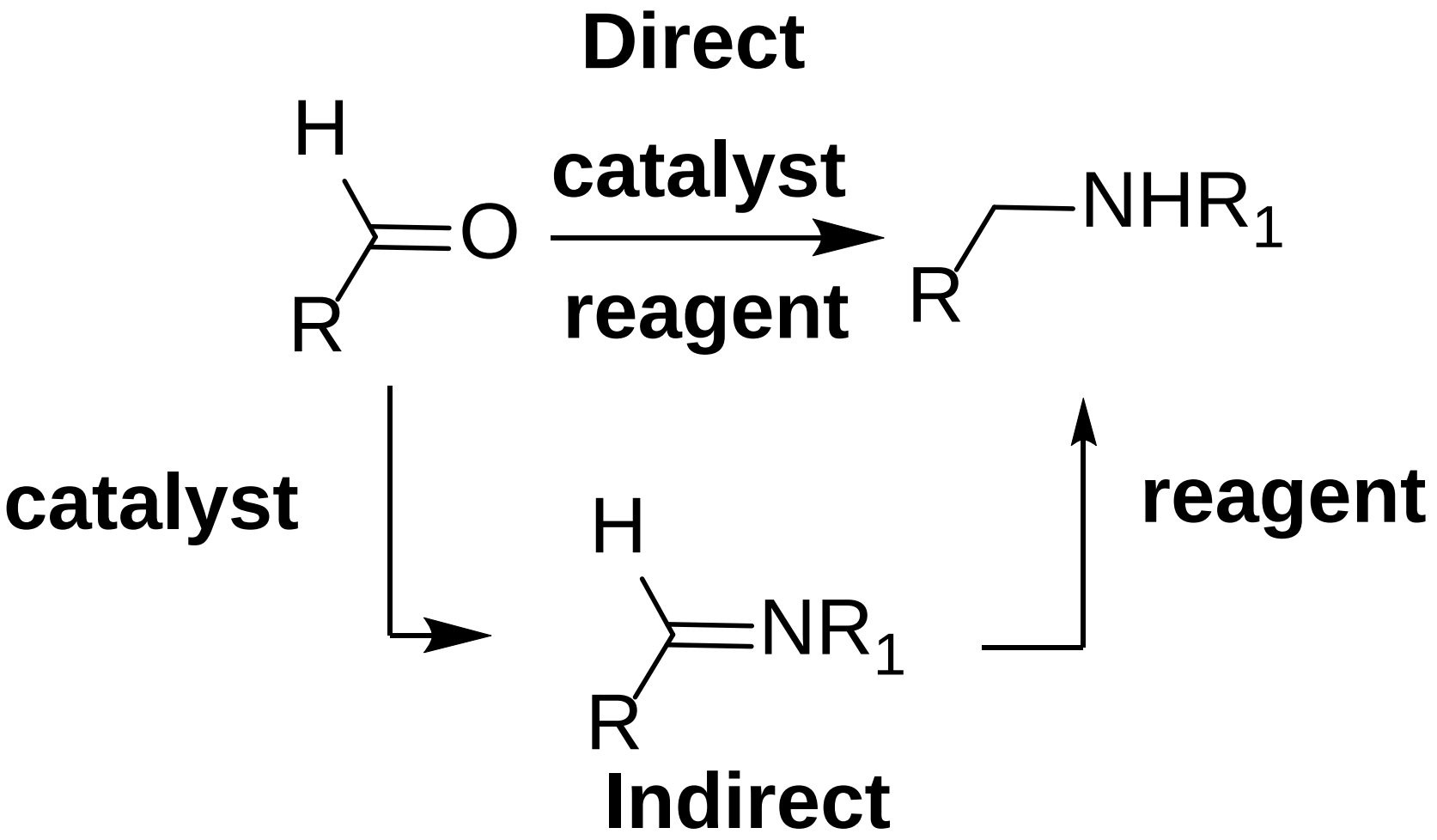
Tetrahedron Lett., **2007**, *48, 8001-8004*

DR. REDDY'S

Types of Innovation

1. Incremental
2. Medium Size
3. Process
4. Technology based
    a. Biocatalysis
    b. Continuous
5. Major

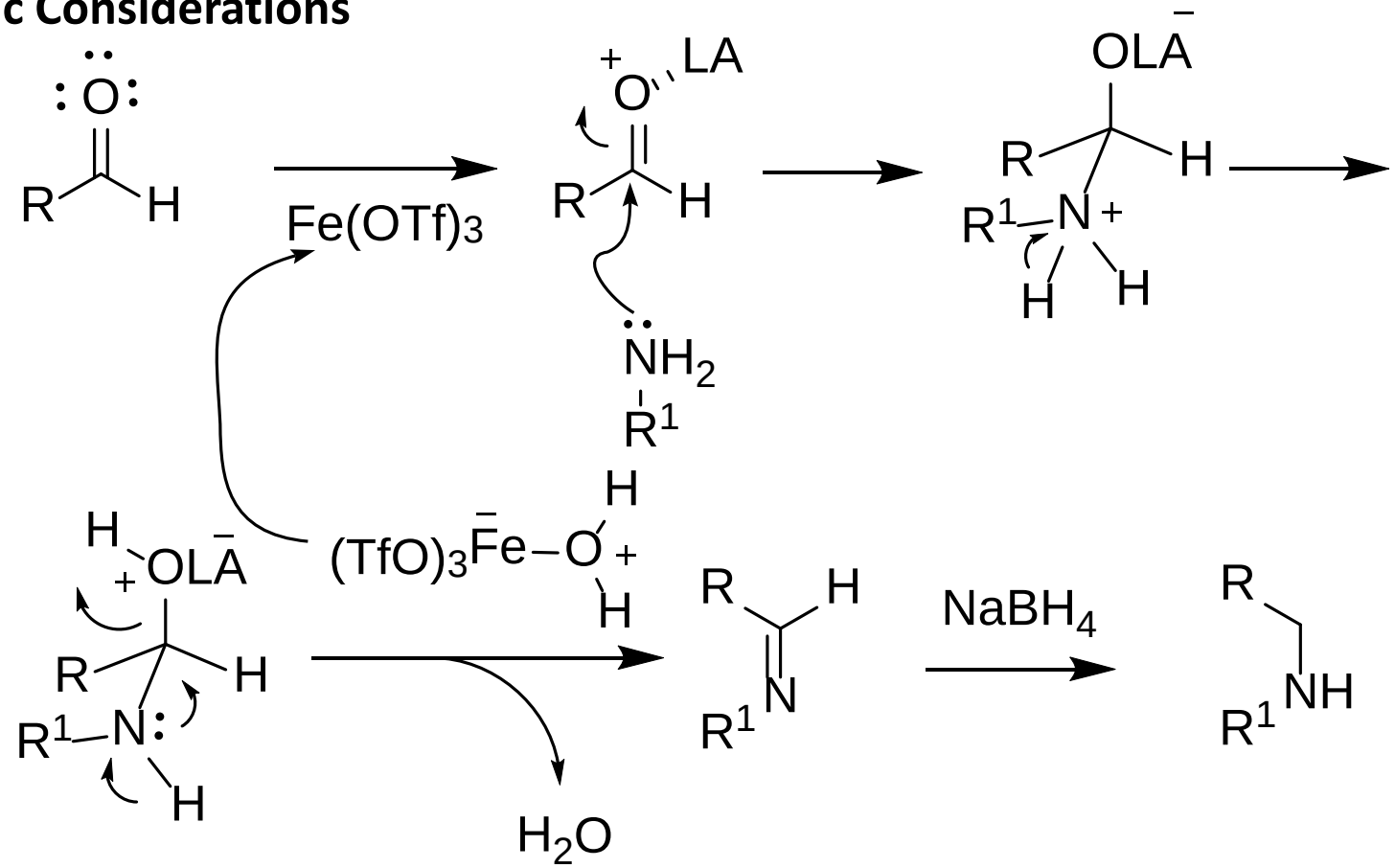
Incremental: Reductive Amination



Kumar, U. Tetrahedron Lett. **2012**, *53,* 4354-4356

Incremental: Reductive Amination

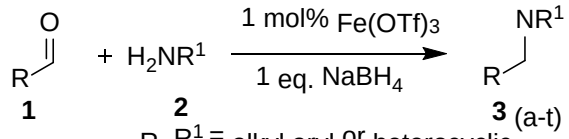
Mechanistic Considerations

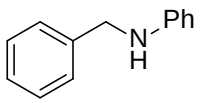


Class 1 (toxic)	Class 2 (less toxic)	Class 3 (non-toxic)
Pt, Pd, Ir, Rh, Ru, Os Mo, Ni, Cr, V	*Cu, Mn, Ti, Sc*	*Zn, Fe*

Incremental: Reductive Amination

Generality of the Method





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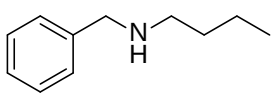
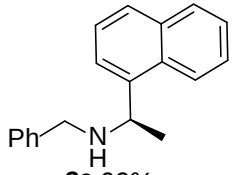


3b 90%



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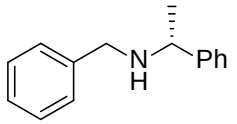
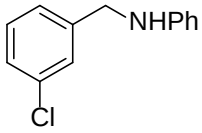
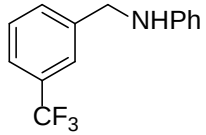


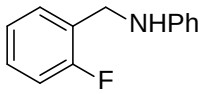
3d 90%



3e 80%



3f 88%



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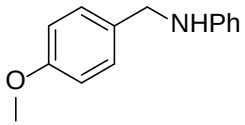
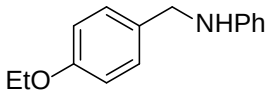
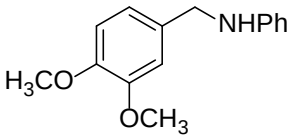


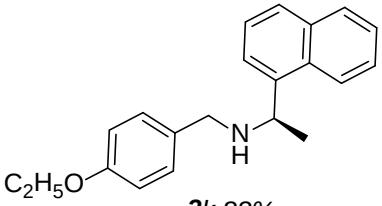
3h 90%



3i 82%



3j 87%



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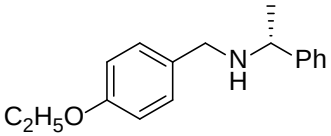
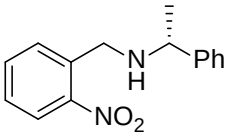
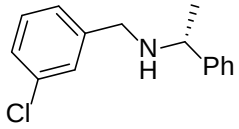


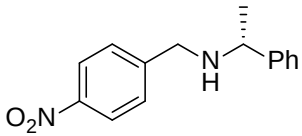
3l 89%



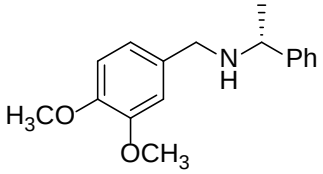
3m 92%



3n 89%



3o 90%



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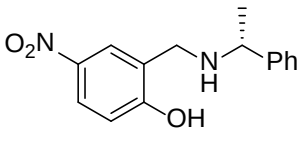

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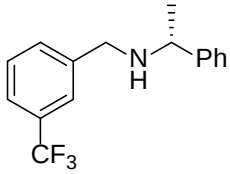
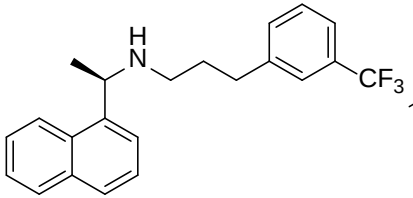
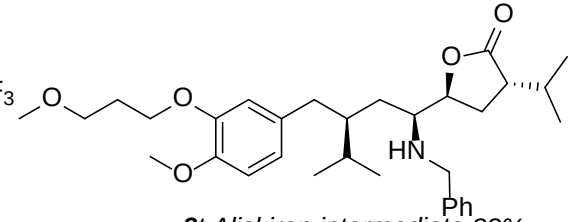


3r 89%

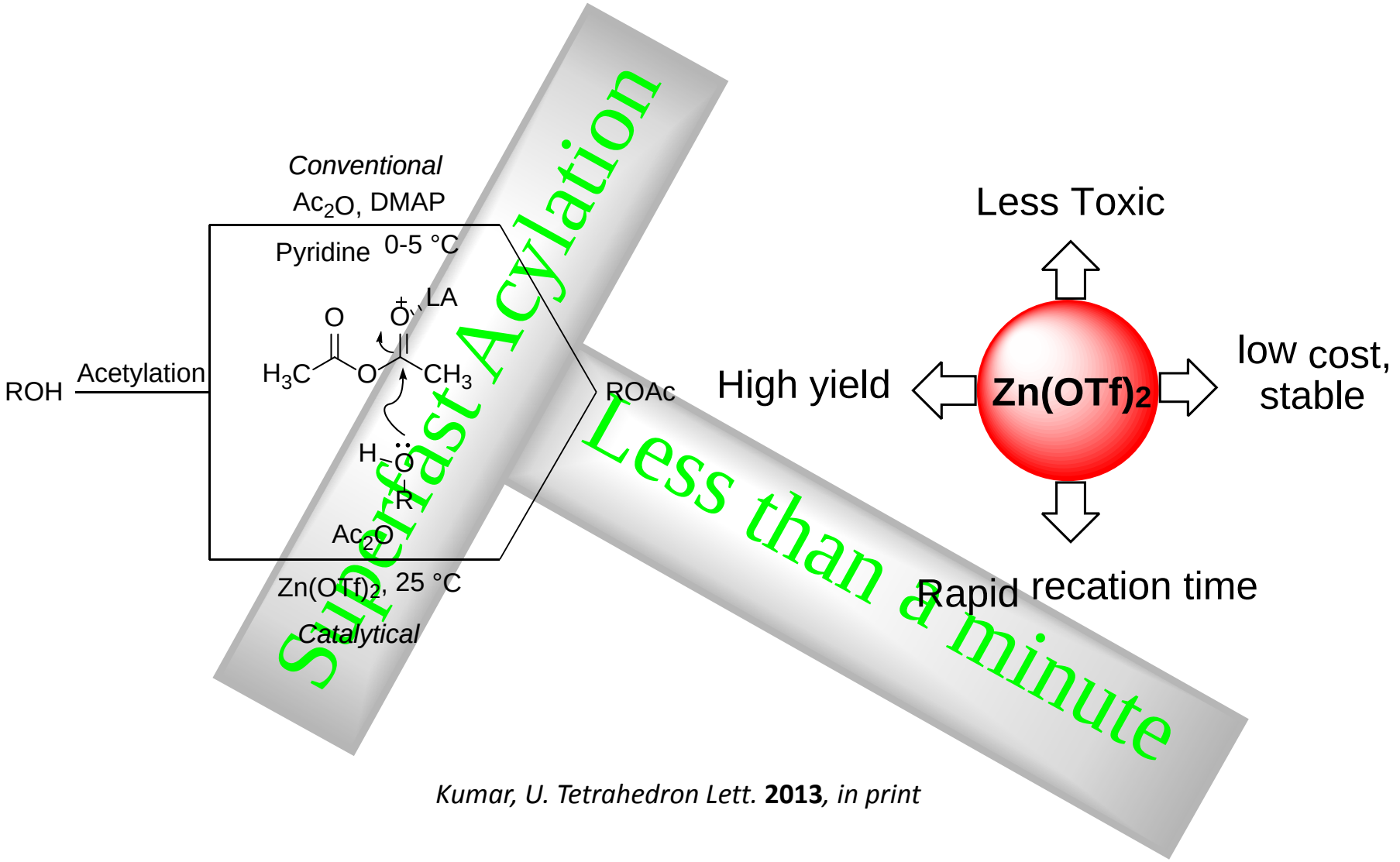


3s Cinacalcet 80%



3t Aliskiren intermediate 88%

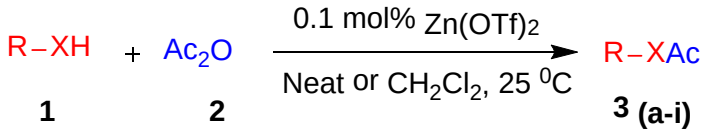
Incremental: Acylation



Kumar, U. Tetrahedron Lett. **2013**, *in print*

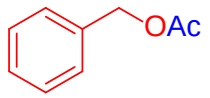
DR. REDDY'S

Generality of the Method

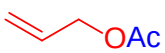


1 **2** **3 (a-i)**

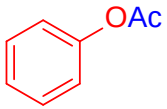
R = alkyl, benzyl, phenyl; X=O, S



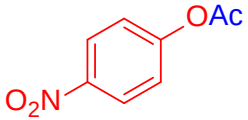
3a 98%



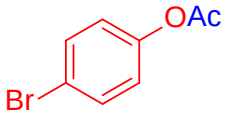
3b 95%



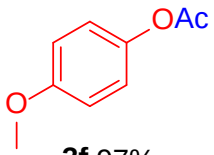
3c 98%



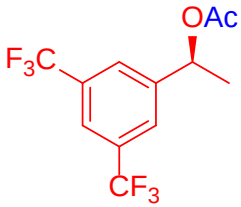
3d 93%



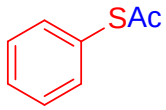
3e 94%



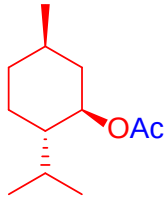
3f 97%



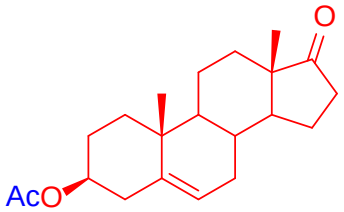
3g 98%



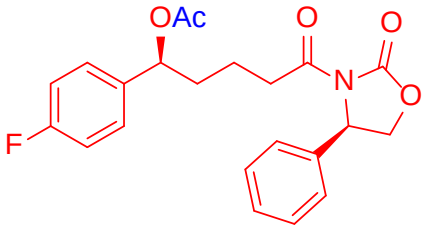
3h 95%



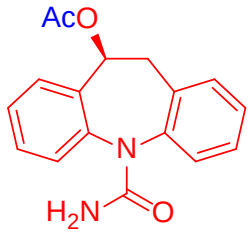
3i 98%



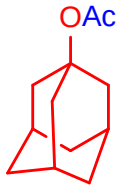
3j 92%



3k 98%



3l 90%



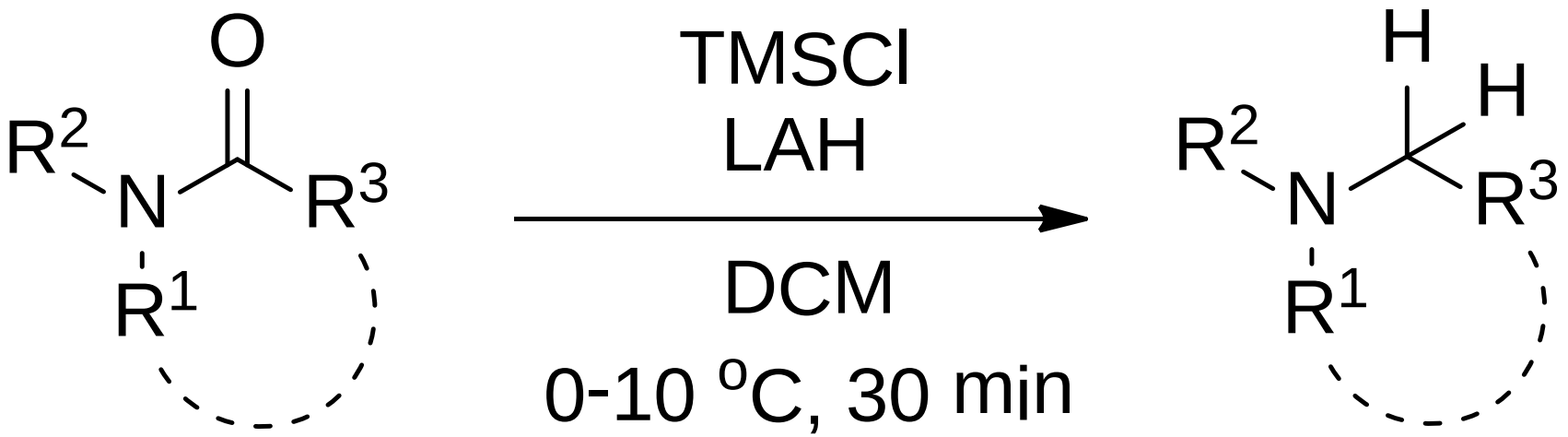
3m 85%

Incremental: Acylation

Pyridine (Py)/AC_2O Mediated vs $Zn(OTf)_2$ Catalyzed Acylation

Substrate	Reagent/catalyst	Conditions	Time	Yield (%)
2l	cat. DMAP, Py/Ac_2O	CH_2Cl_2, Reflux	2 h	90
	$Zn(OTf)_2$ (0.1 mol%) /Ac_2O	25-25 °C	60s	90
2j	Py/Ac_2O	25-25 °C	3 h	87
	$Zn(OTf)_2$ (0.1 mol%) /Ac_2O	25-25 °C	30s	92

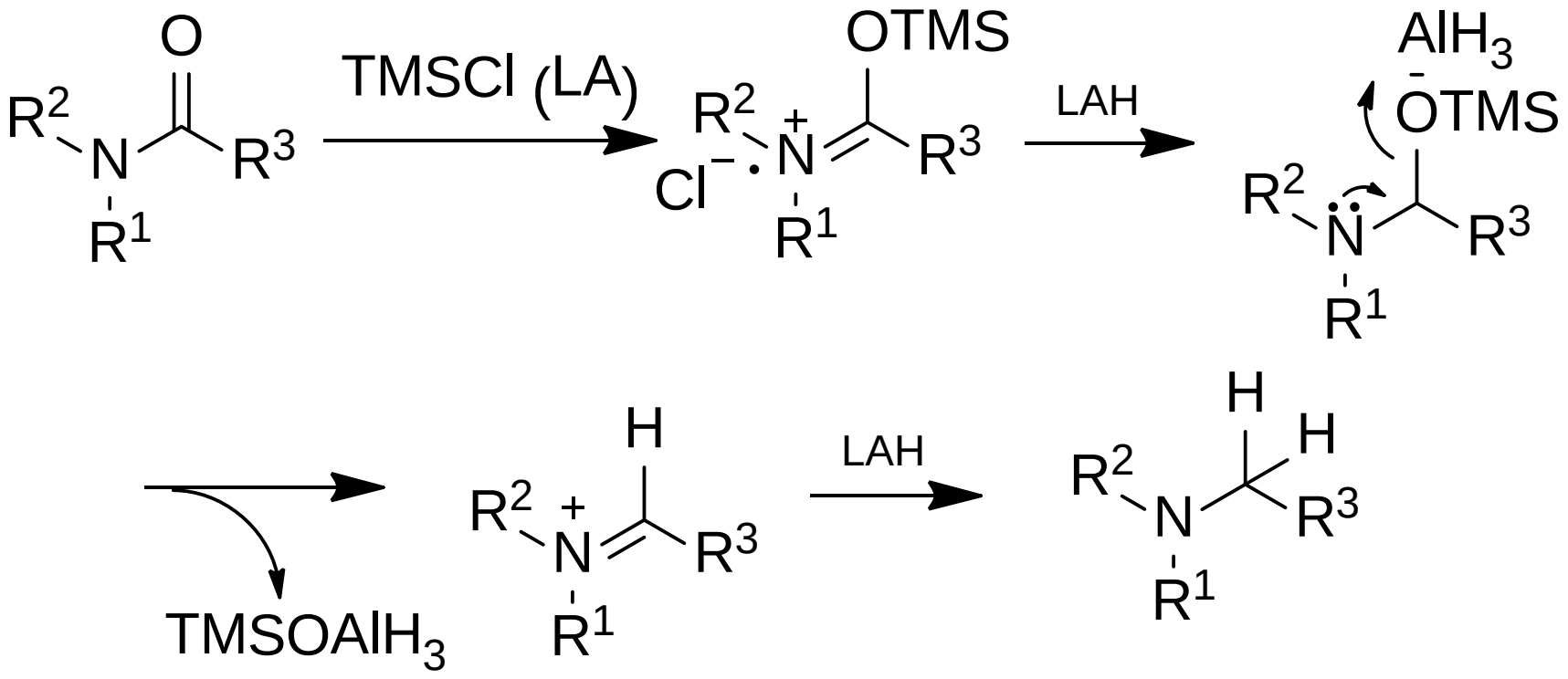
Incremental: Amide Reduction



Tetrahedron Lett. **2013**, *54*, 4908-4913. (Featured in R&D Highlights Published in *Org.Proc.Res.&Dev.* **2013** and being tracked in Article Usage Dashboard)

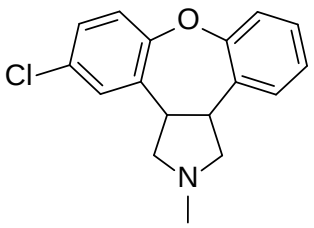
Incremental: Amide Reduction

Mechanistic Considerations

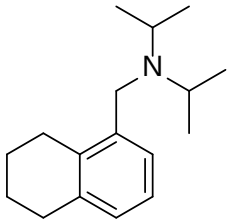


Incremental: Amide Reduction

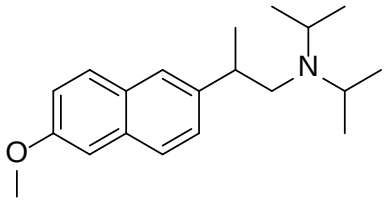
Generality of the Method



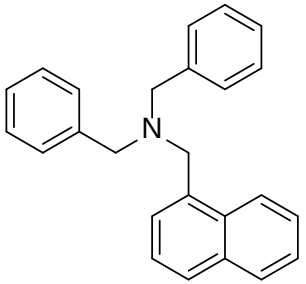
1b, 85%



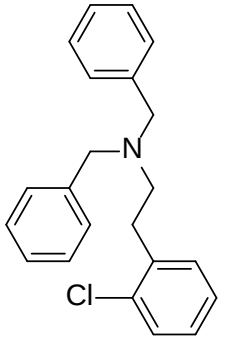
2b, 78%



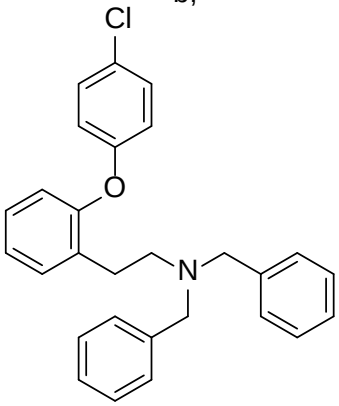
3b, 79%



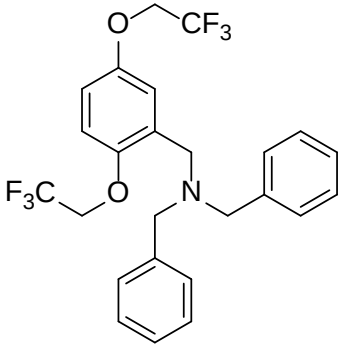
4b, 77%



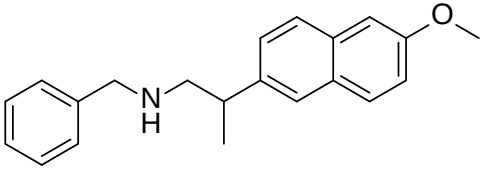
5b, 81%



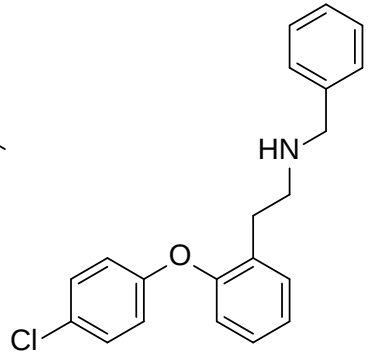
6b, 75%



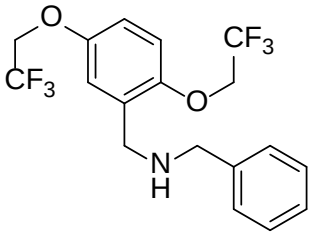
7b, 77%



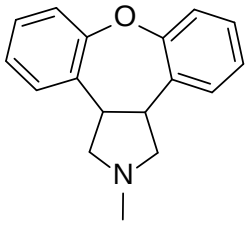
8b, 81%



9b, 74%



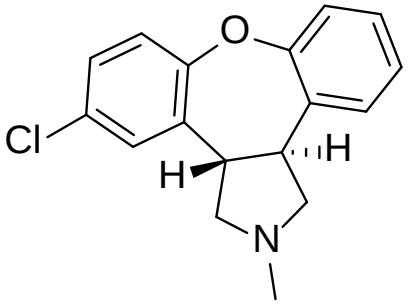
10b, 84%



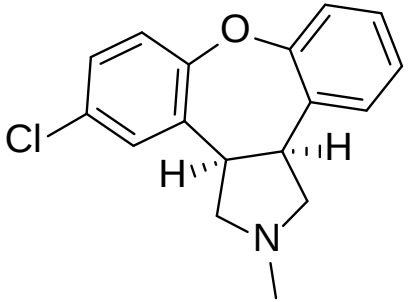
11b, 79%

Incremental: Amide Reduction

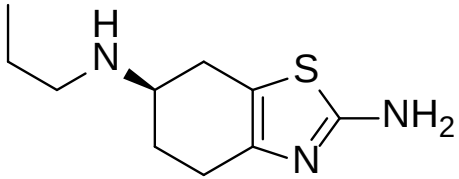
Generality of the Method



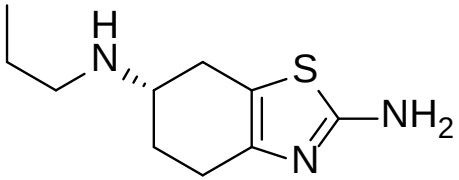
1b', 85%, 99% *de*



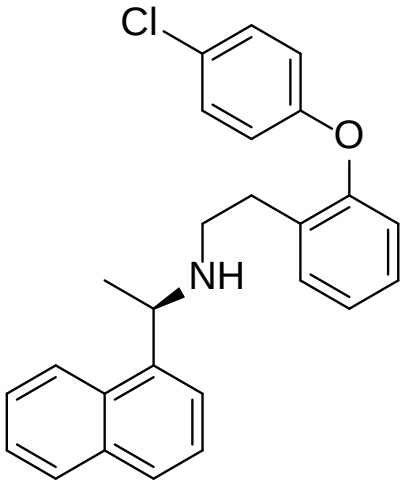
1b'', 79%, 99% *de*



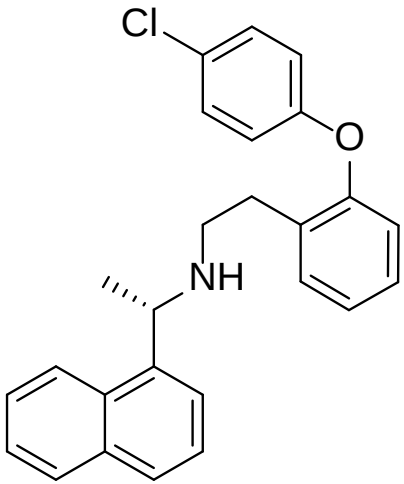
12b, 77%, 98.5% *ee*



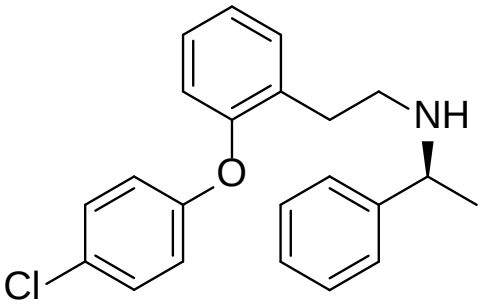
13b, 72%, 98.5% *ee*



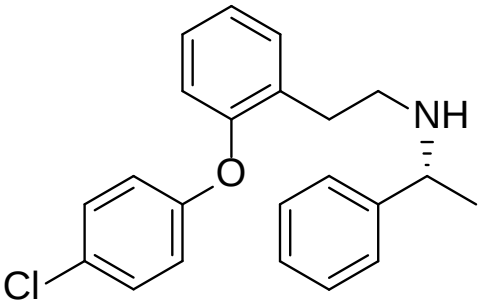
14b, 81%, 99% *ee*



15b, 79%, 99% *ee*



16b, 82%, 98.5% *ee*



17b, 79%, 98.5% *ee*

Incremental: Amide Reduction

Article Usage Dashboard

Amide activation by TMSCl: reduction of amides to amines by LiAlH"4 under mild conditions

Ravinder, B.; Rajeswar Reddy, S.; Panasa Reddy, A.; Bandichhor, R.

Tetrahedron Letters, Volume(s) 54, 04-Jul-2013, Pages 4908-4913

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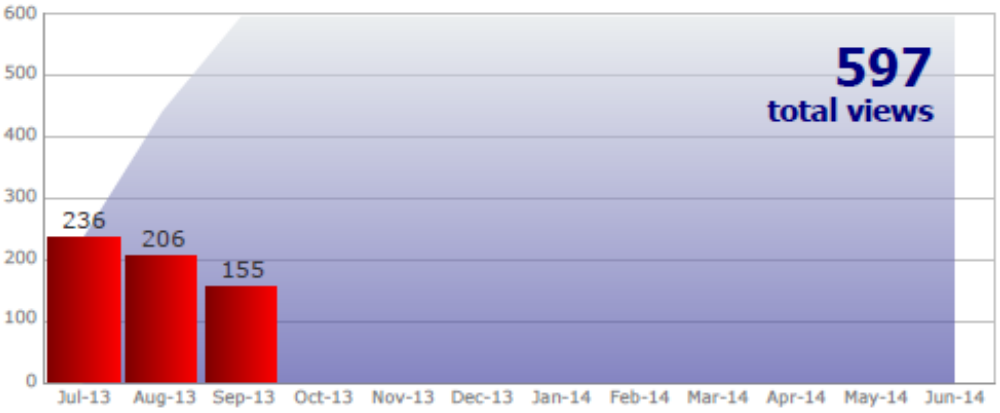

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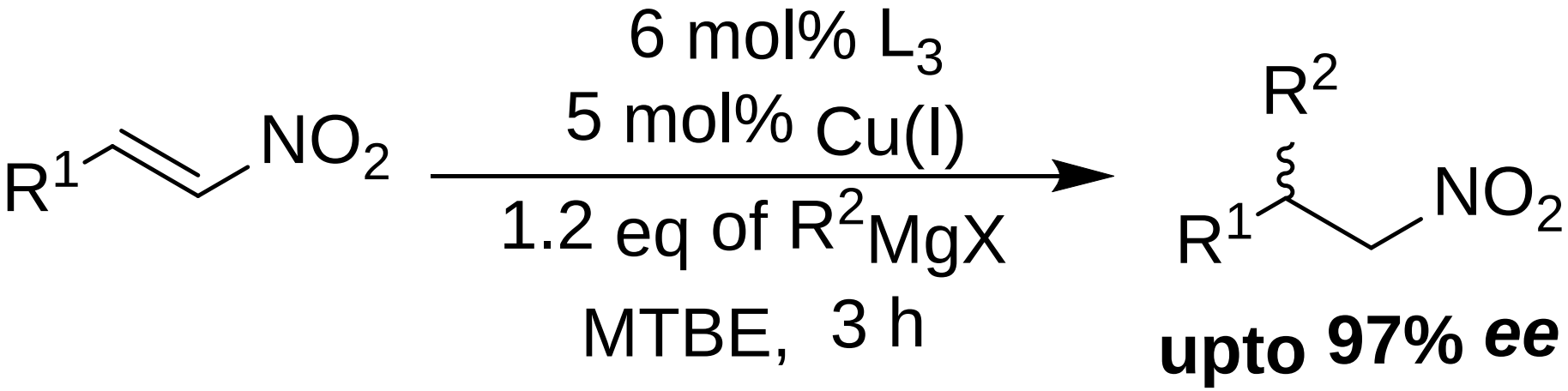
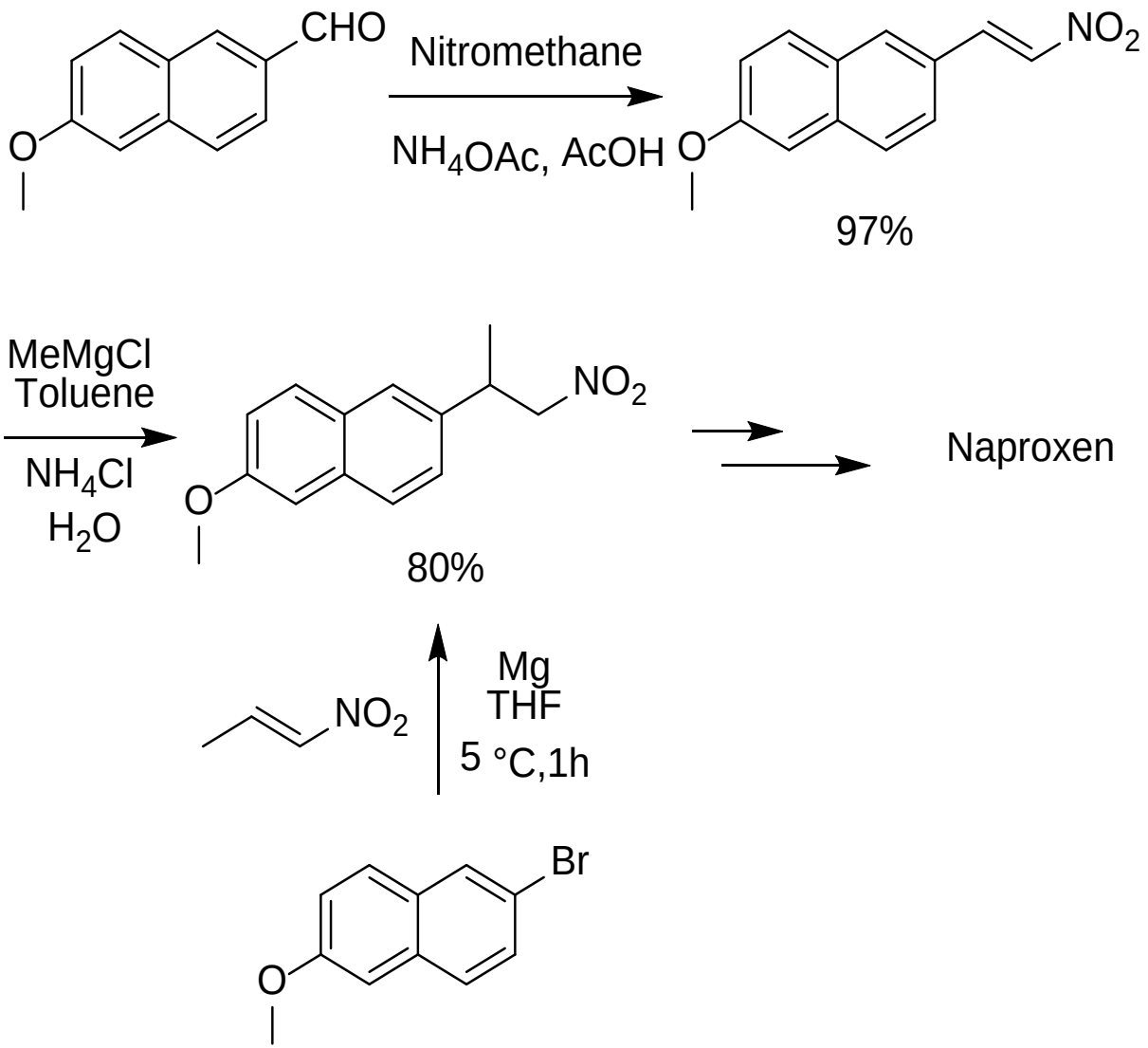


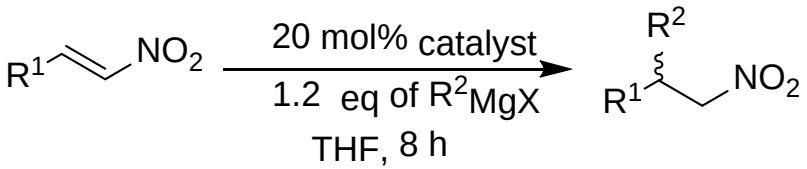
Prashanth Reddy, G. *Tetrahedron Lett*., **2013**, 54, 3911-3915

Potential Application

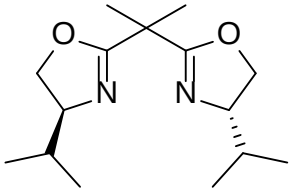


Medium Size: Enantioselective Grignard Addition to Nitroolefin

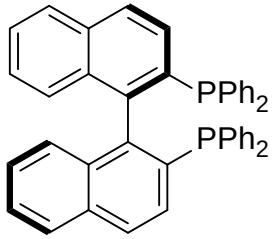
Screening



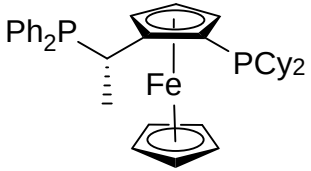
S.No.	Catalyst	$R^1/R^2/X$	˚C	*er (R/S)* (HPLC)	Yield (%)
1	CuTC/L_1	6Mn/Me/Br	-60	49.5/50.5	75
2	CuTC/L_1	6Mn/Me/Br	-20	49/51	75
3	CuI/L_1	6Mn/Me/Br	-60	45/55	70
4	CuI/L_1	6Mn/Me/Br	-20	48.6/51.4	70
5	$Zn(OTf)_2/L_1$	6Mn/Me/Br	-60	49.5/50.5	70
6	$Zn(OTf)_2/L_1$	6Mn/Me/Br	-20	49.5/50.5	70
7	CuTC/L_2	6Mn/Me/Br	-60	49/51	75
8	CuTC/L_2	6Mn/Me/Br	-20	49.5/50.5	75
9	CuI/L_2	6Mn/Me/Br	-60	49.3/50.7	70
10	CuI/L_2	6Mn/Me/Br	-20	49.7/50.3	70
11	$Zn(OTf)_2/L_2$	6Mn/Me/Br	-60	49.2/50.8	70
12	$Zn(OTf)_2/L_2$	6Mn/Me/Br	-20	49.6/50.4	70
13	CuTC/L_1	6Mn/Me/Cl	-70	49.2/50.8	70
14	CuTC/L_1	6Mn/Me/Cl	-20	49.3/50.7	70
15	CuTC/L_1	6Mn/Me/Cl	-35	48/52	72



L_1: (*SS*)-isopropyl bisoxazoline



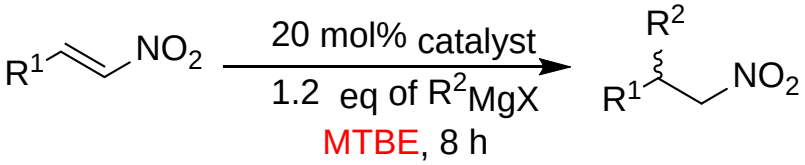
L_2: (*R*)-BINAP



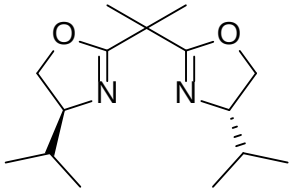
L_3: [(*S*)-1-[(Rp)-2-(Dicyclohexyl-phosphino)-ferrocenylethyl]di phenylphosphine]

Medium Size: Enantioselective Grignard Addition to Nitroolefin

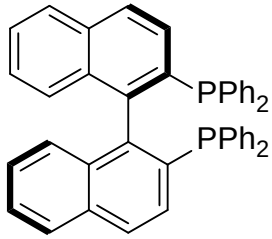
Screening



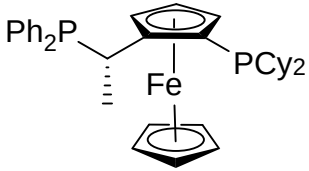
S.No.	Catalyst	$R^1/R^2/X$	°C	*er* (*R*/*S*) (HPLC)	Yield %
1	$CuTC/L_1$	6Mn/Me/Cl	-40	48.7/51.3	70
2	$CuTC/L_1$	6Mn/Et/Cl	-40	49/51	69
3	$CuTC/L_1$	6Mn/^{i}Pr/Cl	-40	51/49	67
4	**$CuTC/L_1$**	**6Mn/^{t}Bu/Cl**	**-40**	**72/28**	**68**
5	**$CuTC/L_1$**	**6Mn/^{t}Bu/Cl**	**-70**	**77/23**	**69**



L_1: (*SS*)-isopropyl bisoxazoline



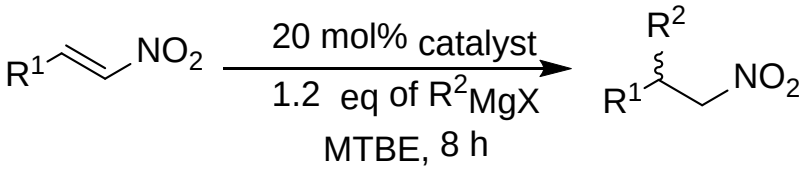
L_2: (*R*)-BINAP



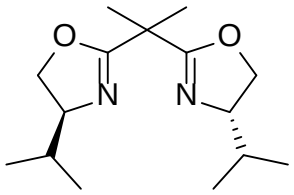
L_3: [(*S*)-1-[(Rp)-2-(Dicyclohexyl-phosphino)-ferrocenylethyl]di phenylphosphine]

Medium Size: Enantioselective Grignard Addition to Nitroolefin

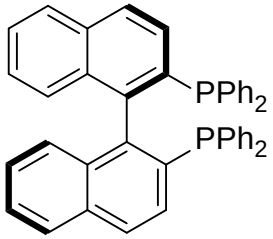
Screening



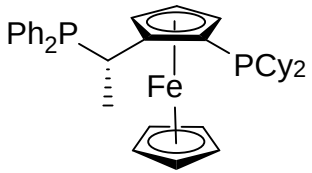
S.No.	Catalyst	$R^1/R^2/X$	°C	*er (R/S) (HPLC)*	Yield %
1	CuI/L_3	6Mn/Me/Cl	-70	*49.2/50.8*	68
2	CuI/L_3	6Mn/Et/Cl	-70	*49.5/50.5*	64
3	CuI/L_3	6Mn/^{i}Pr/Cl	-70	*51.97/48.03*	64
4	CuTC/L_3	6Mn/^{t}Bu/Cl	-70	*61/39*	62
5	**CuI/L_3**	**6Mn/^{t}Bu/Cl**	**-70**	***98.5/1.5***	**62**
6	**CuI/L_3**	**6Mn/^{t}Bu/Cl**	**-70**	***97.9/2.1***	**64**
7	**CuI/L_3**	**6Mn/^{t}Bu/Cl**	**-70**	***97.9/2.1***	**65**
8	**CuI/L_3**	**6Mn/^{t}Bu/Cl**	**-70**	***97.8/2.2***	**63**
9	CuI/L_3	^{i}Bu/6Mn/Br	-70	*25/75*	75
10	CuTC/L_3	6Mn/Ph/Cl	-70	50.56/49.44	62
11	CuTC/L3	6Mn/Benzyl/Cl	-70	49.49/50.51	66
12	CuI/L_3	Ph/^{t}Bu/Cl	-70	*39.5/60.5*	60
13	CuI/L_3	*p*-EtO-Ph/^{t}Bu/Cl	-70	*23/77*	65
14	**CuI/L_3**	***p*-F-Ph/^{t}Bu/Cl**	**-70**	***4/96***	**60**



L_1: (*SS*)-isopropyl bisoxazoline



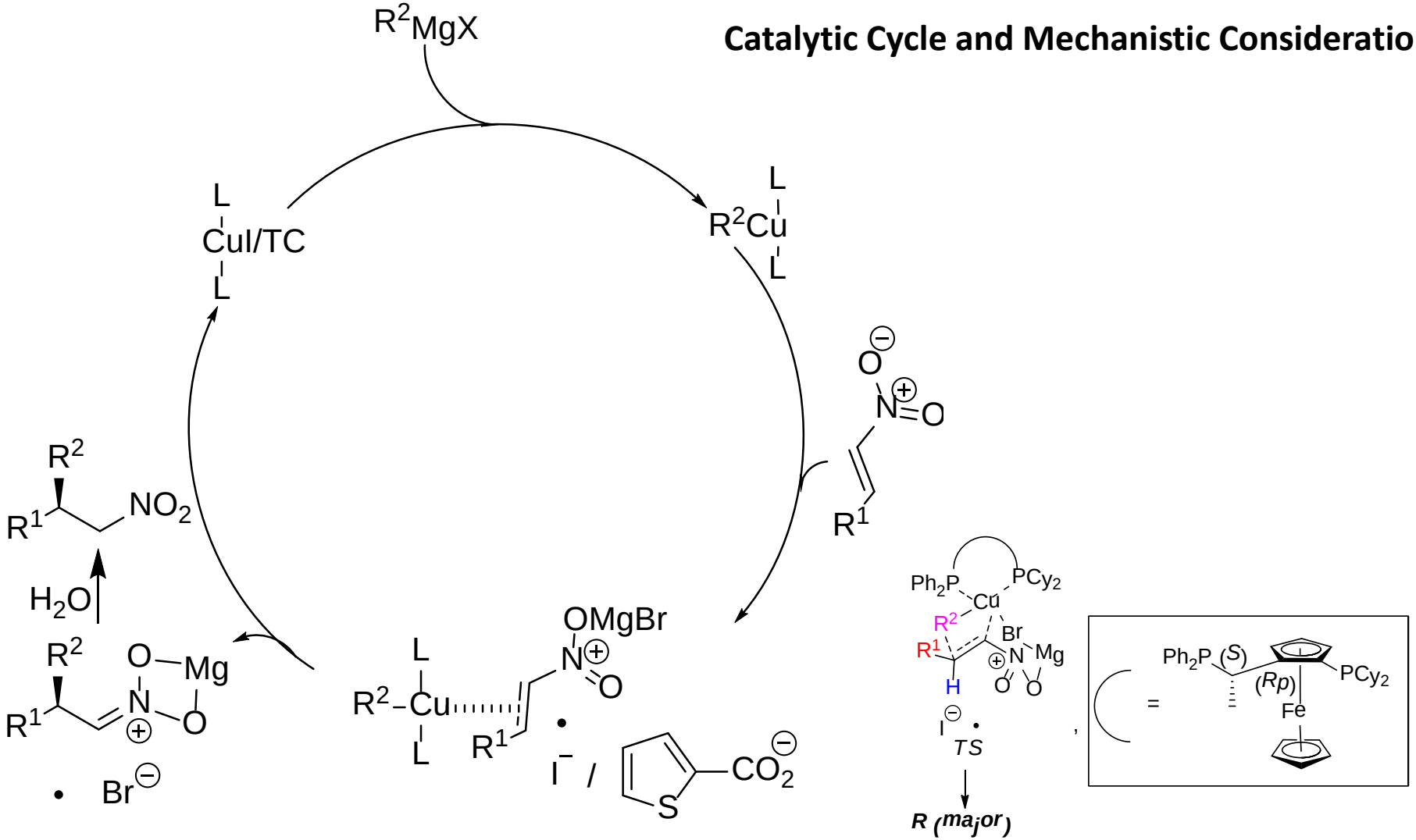
L_2: (*R*)-BINAP



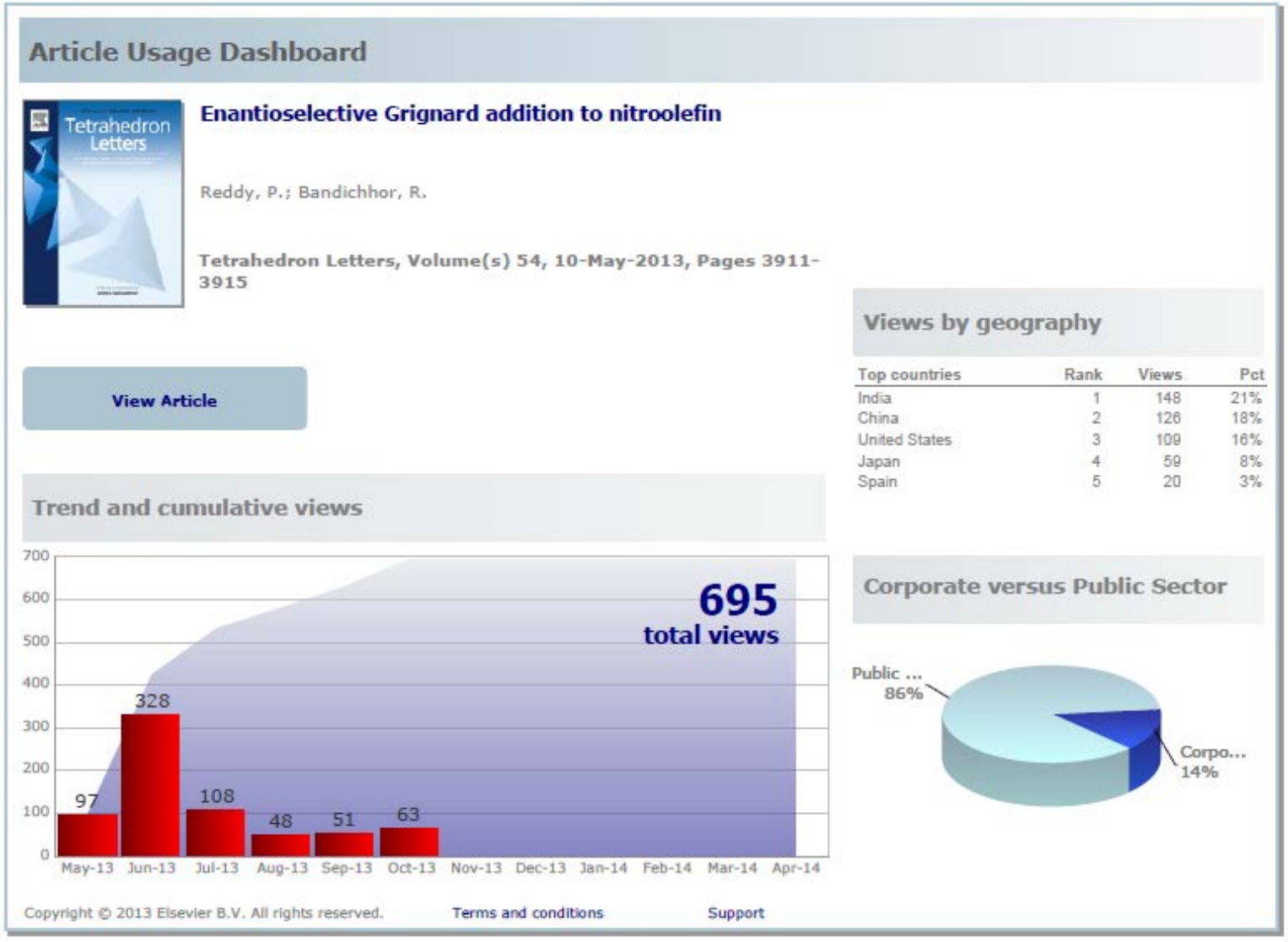
L_3: [(*S*)-1-[(Rp)-2-(Dicyclohexyl-phosphino)-ferrocenylethyl]diphenylphosphine]

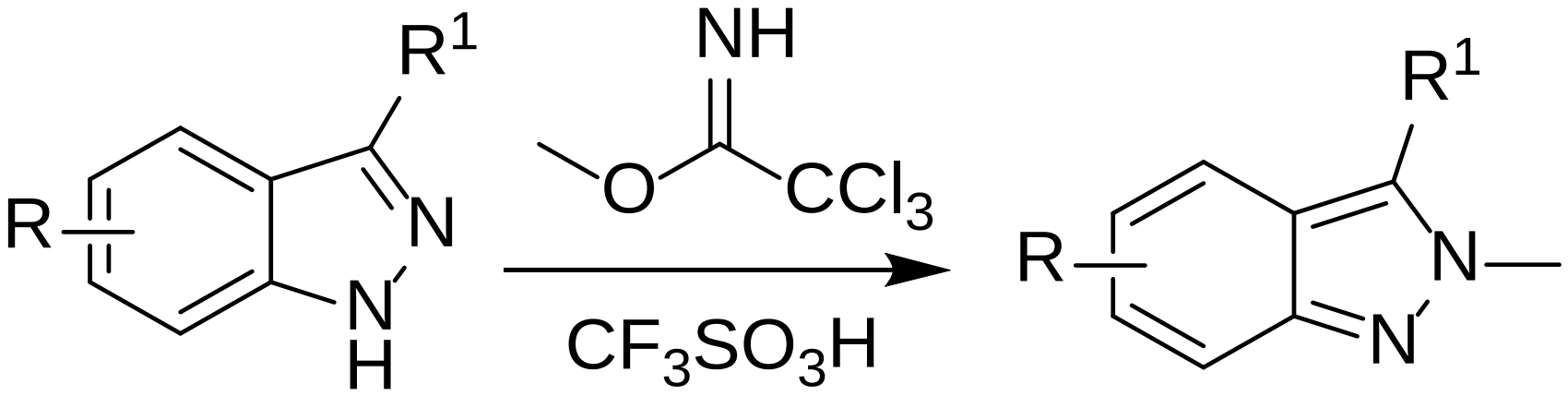
Medium Size: Enantioselective Grignard Addition to Nitroolefin

Catalytic Cycle and Mechanistic Consideration



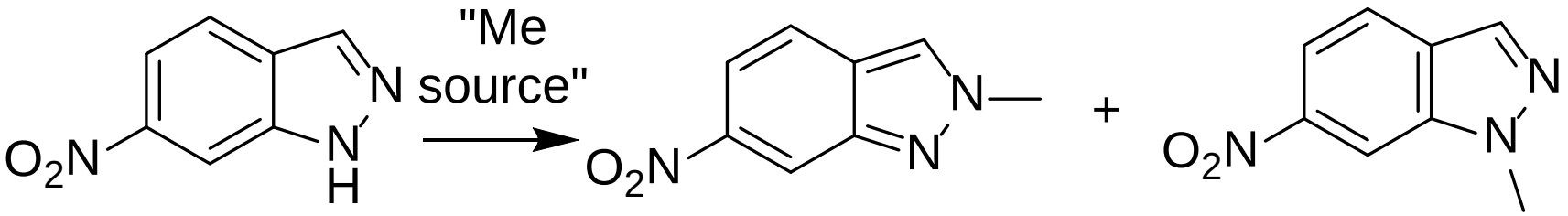
Medium Size: Enantioselective Grignard Addition to Nitroolefin





Sudhakar, *Tetrahedron Lett*., **2013**, *54*, 1661-1663

Different Methods



1

2

N-2 product

2*H*-indazole

3

N-1 product

1*H*-indazole

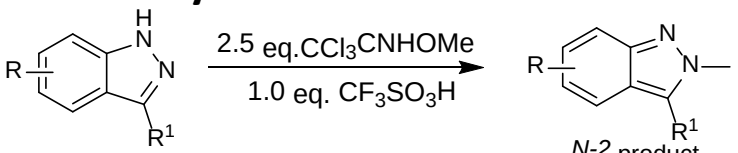
Basic condition: No selectivity

Acidic condition: N-1 (thermodynamic); N-2 (kinetic)

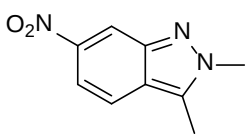
Trimethyloxonium tetrafluoroborate (Meerwein's reagent) is considered to be the best reagent for regioselective methylation

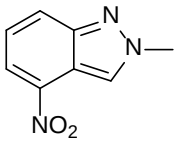
Medium Size: Regioselective Methylation

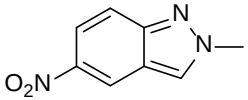
Generality of the Methods

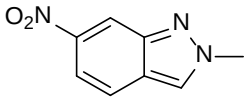


7 (**a-k**) *N-2* product **5** (**a-k**)


87%
5a


96%
5b


97%
5c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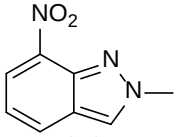
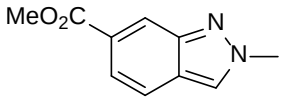
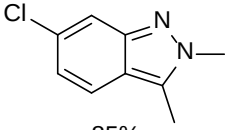
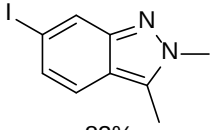
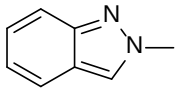
5d

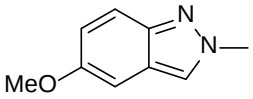

94%
5e

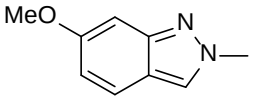

87%
5f

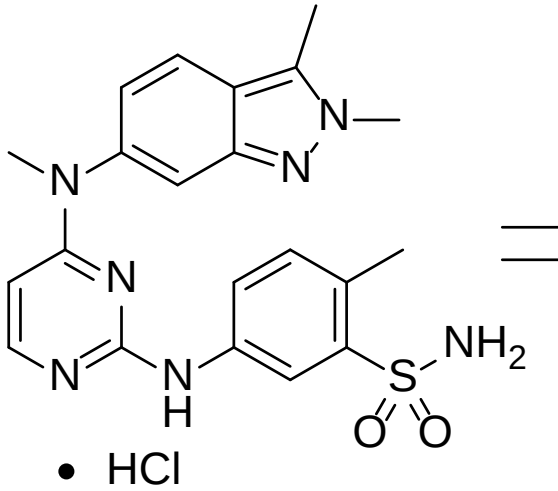

85%
5g


83%
5h

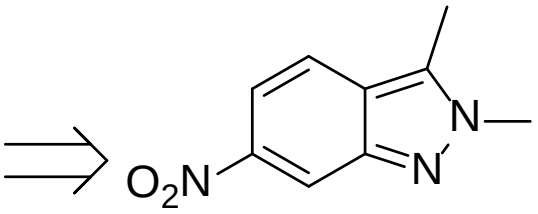

79%
5i


90%
5j

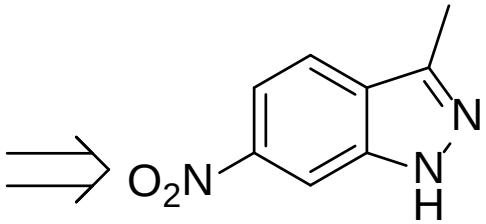

78%
5k


• HCl

4



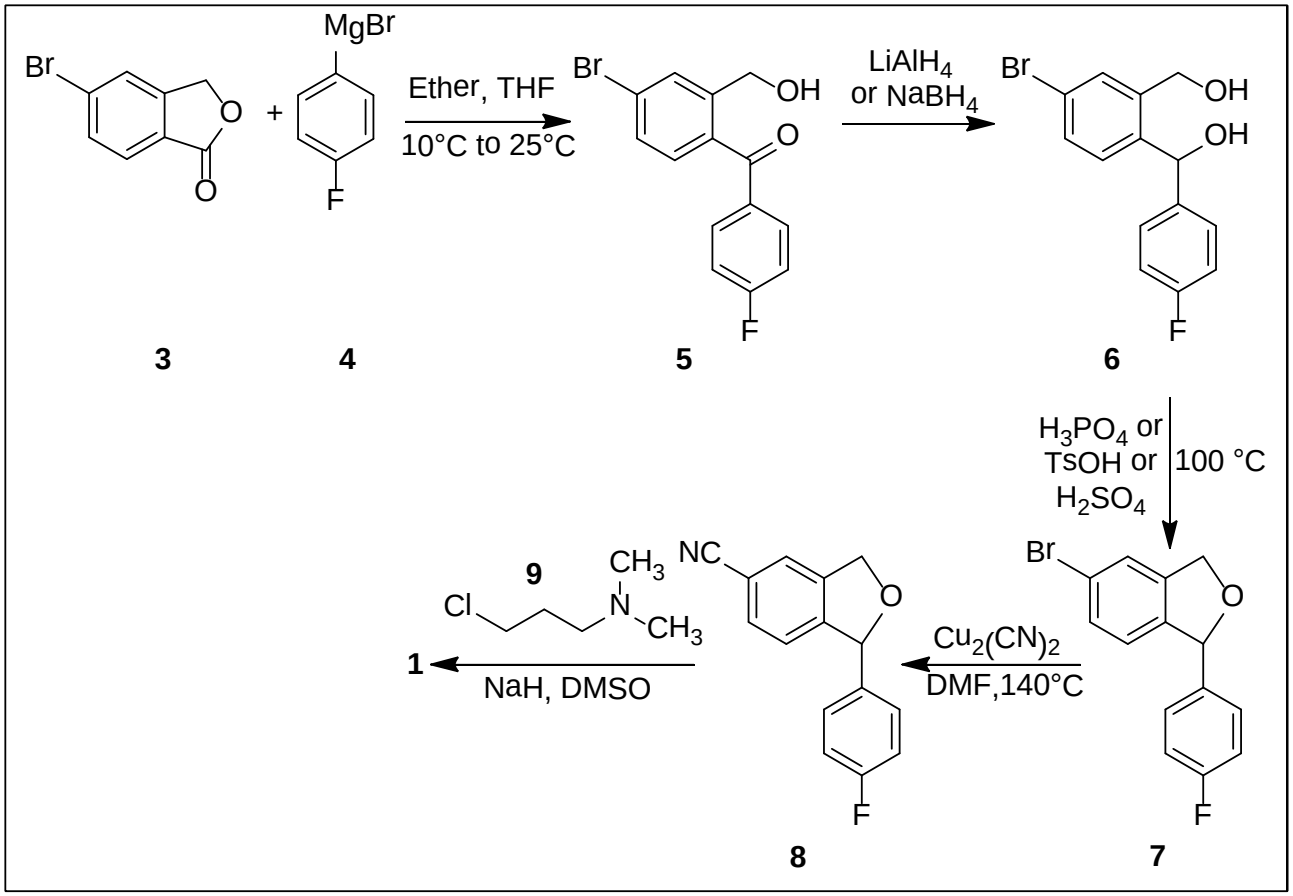
5a

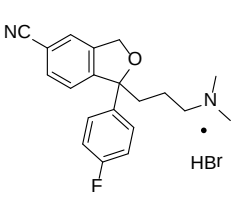


6

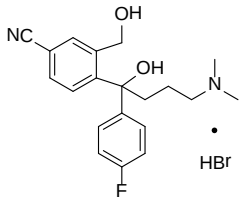
This reagent is suitable to both EWG and EDG containing substrates

First reported synthesis of Citalopram 1





1



2

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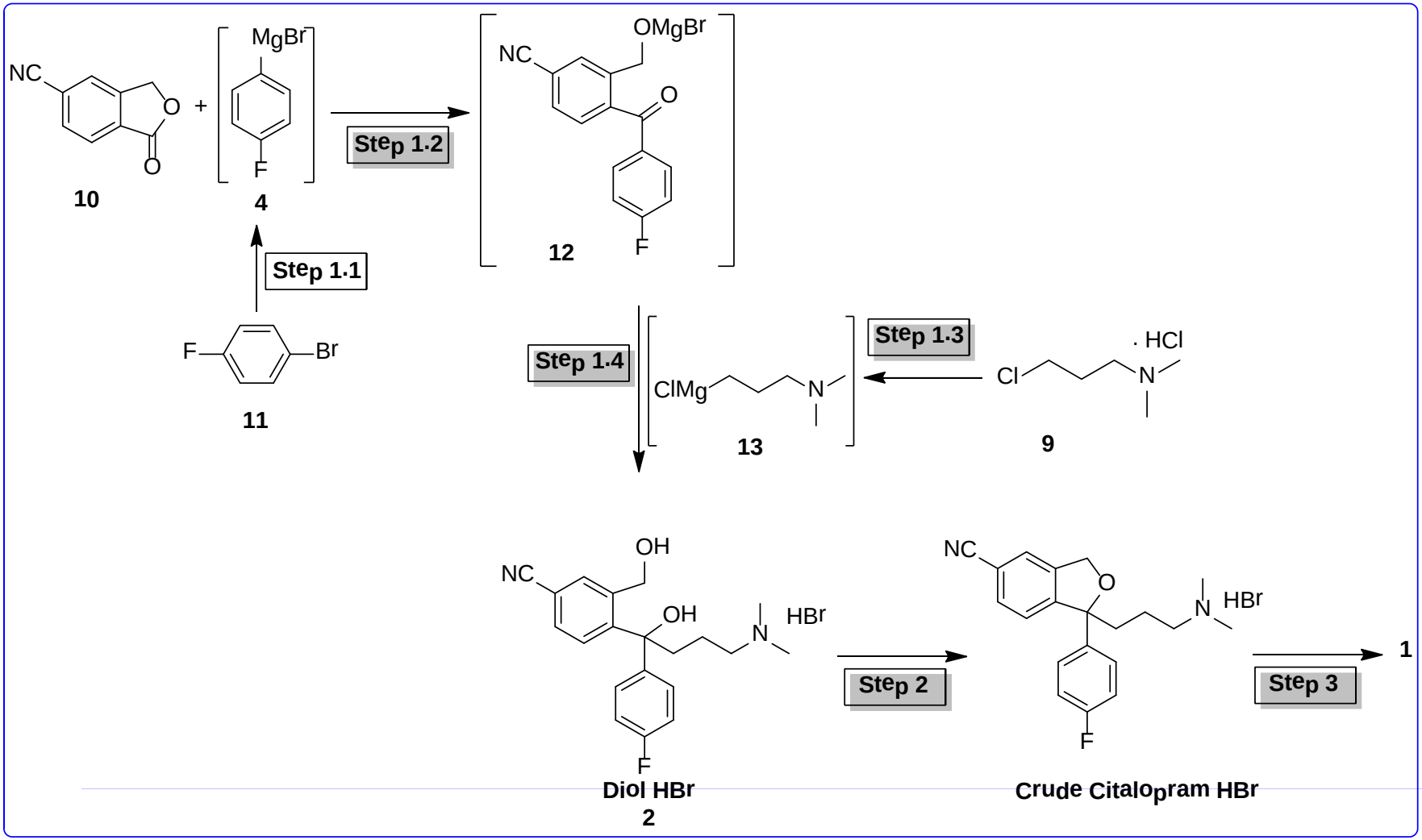
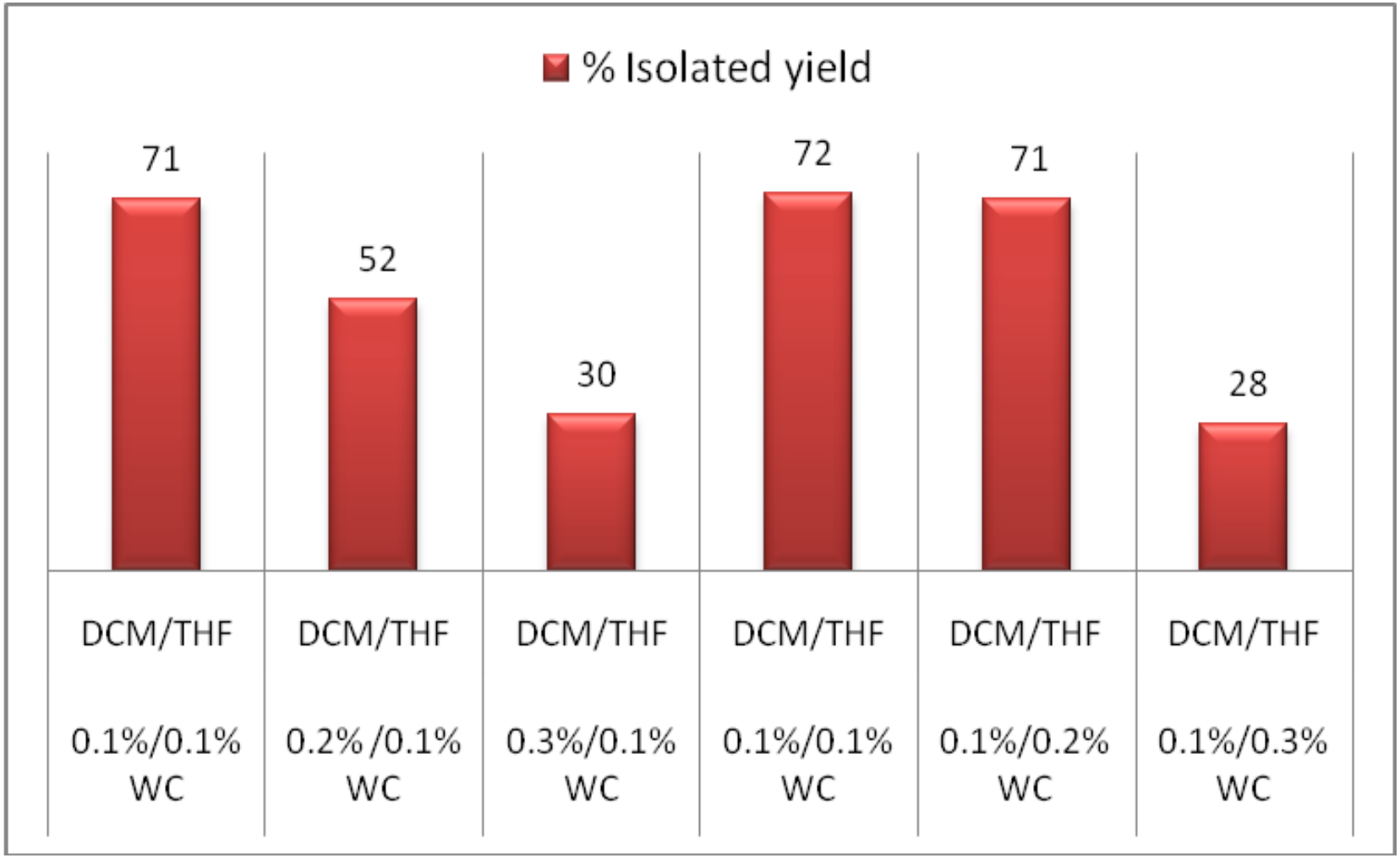
Strategies for Process Improvements

1. Can we freshly prepare GR and use it *in situ?*
2. Can we avoid the use of LAH or Sodium borohydride reagent?
3. Can we avoid Copper cyanide?
4. Can we avoid NaH during alkylation?
5. Can we do most of the transformations at room temperature or at least can we avoid higher temperature (>100 ^{0}C) ?
6. Is it possible to telescope this process to all possible extent?
7. ……etc

Outline Towards Realizing the Strategies : One Pot Synthesis of Diol HBr

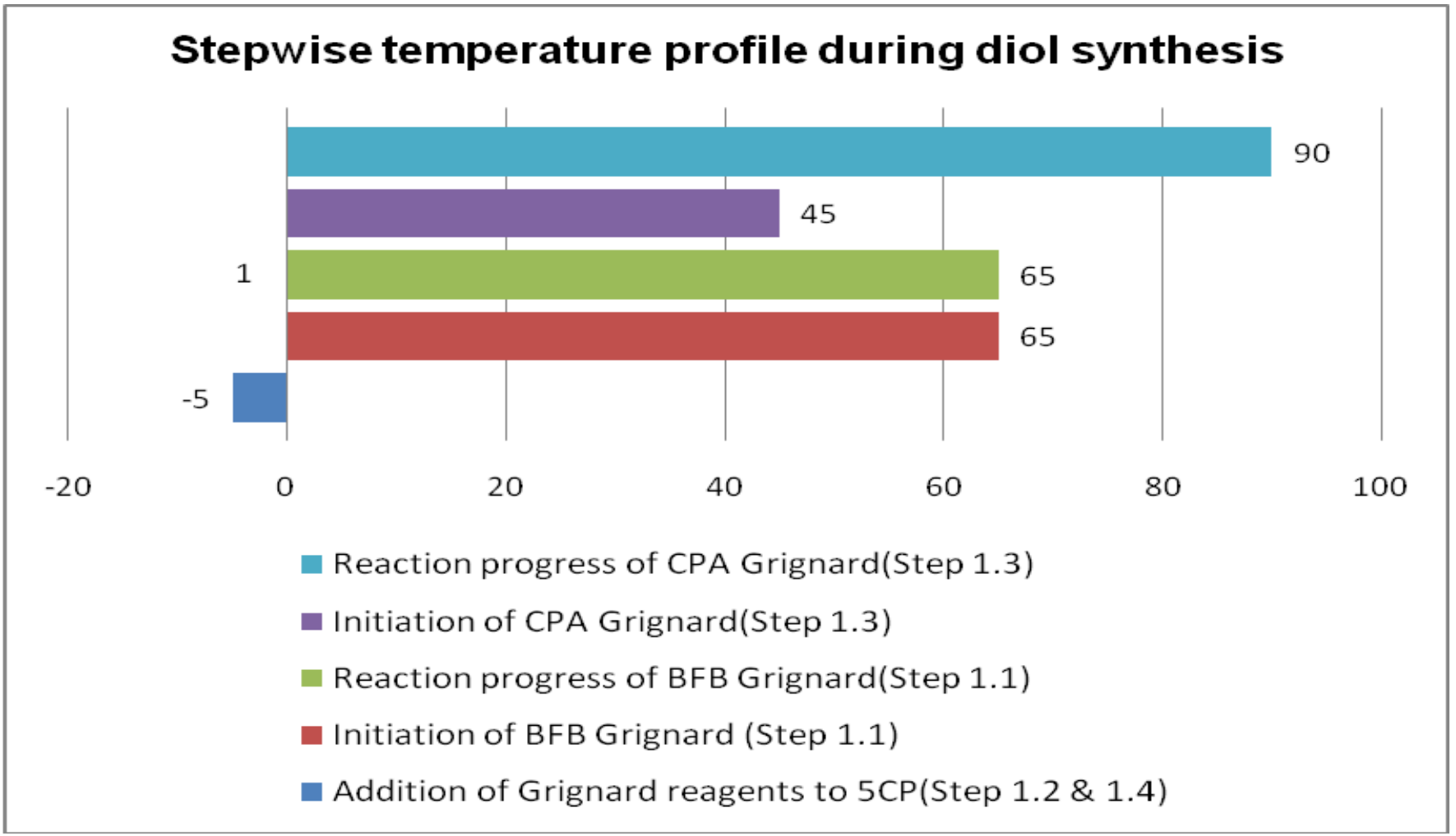


Role of Solvents and Inherent KF



Process Innovation: Grignard Reaction

Temperature Profile



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DoE: Full Factorial

1. Pre DoE experiments
2. Based on domain knowledge, deciding on the variable and response factors
3. Use of software e.g. Design Expert
4. Augmentation of initial results with the help of Response Surface Model to arrive on the optimal conditions
5. Analysis of results by considering ANOVA variance method to derive significant model

Operable ranges for DoE based on pre-DoE experiments

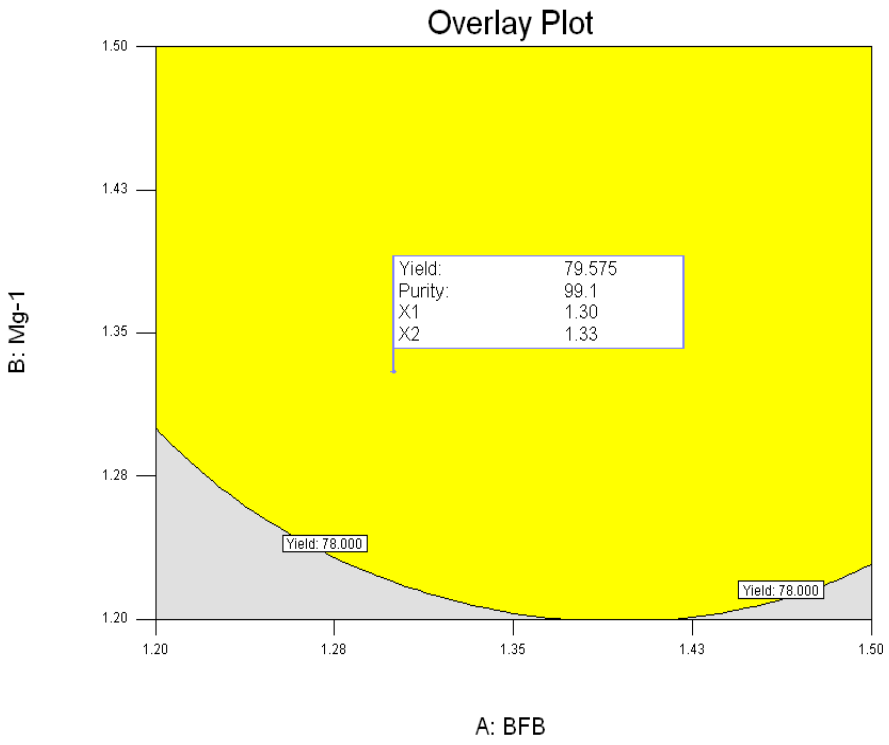
process variables	low	high
BFB (mol equiv.)	1.2	1.5
Mg (mol equiv.)	1.2	1.5
Iodine (% w/w)	1	10

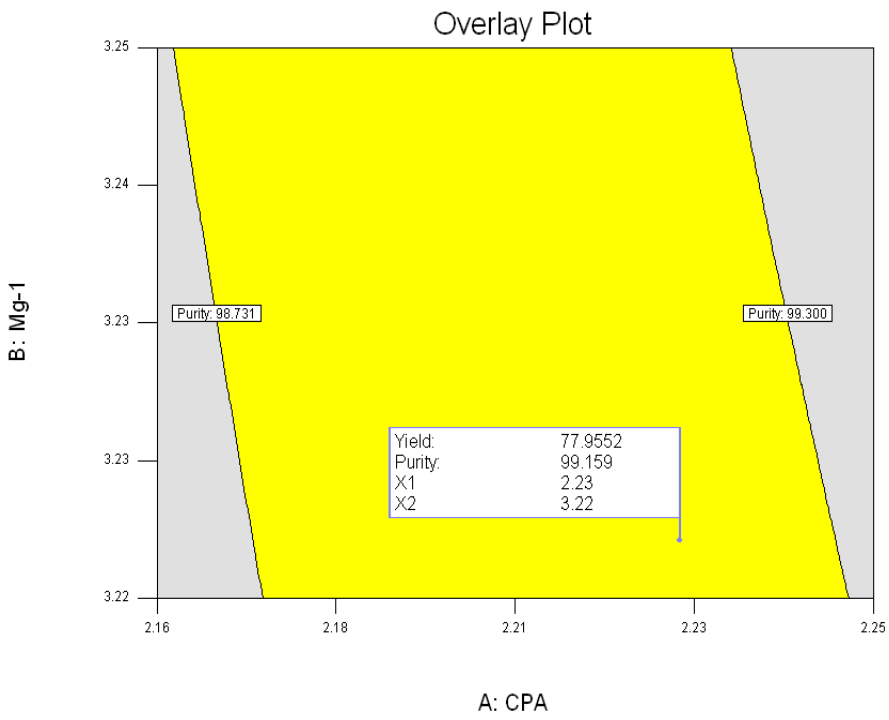
process variables	low	high
CPA (mol equiv.)	1.8	3.0
Mg (mol equiv.)	2.0	4.0
Iodine (% w/w)	1	10

Response Factors

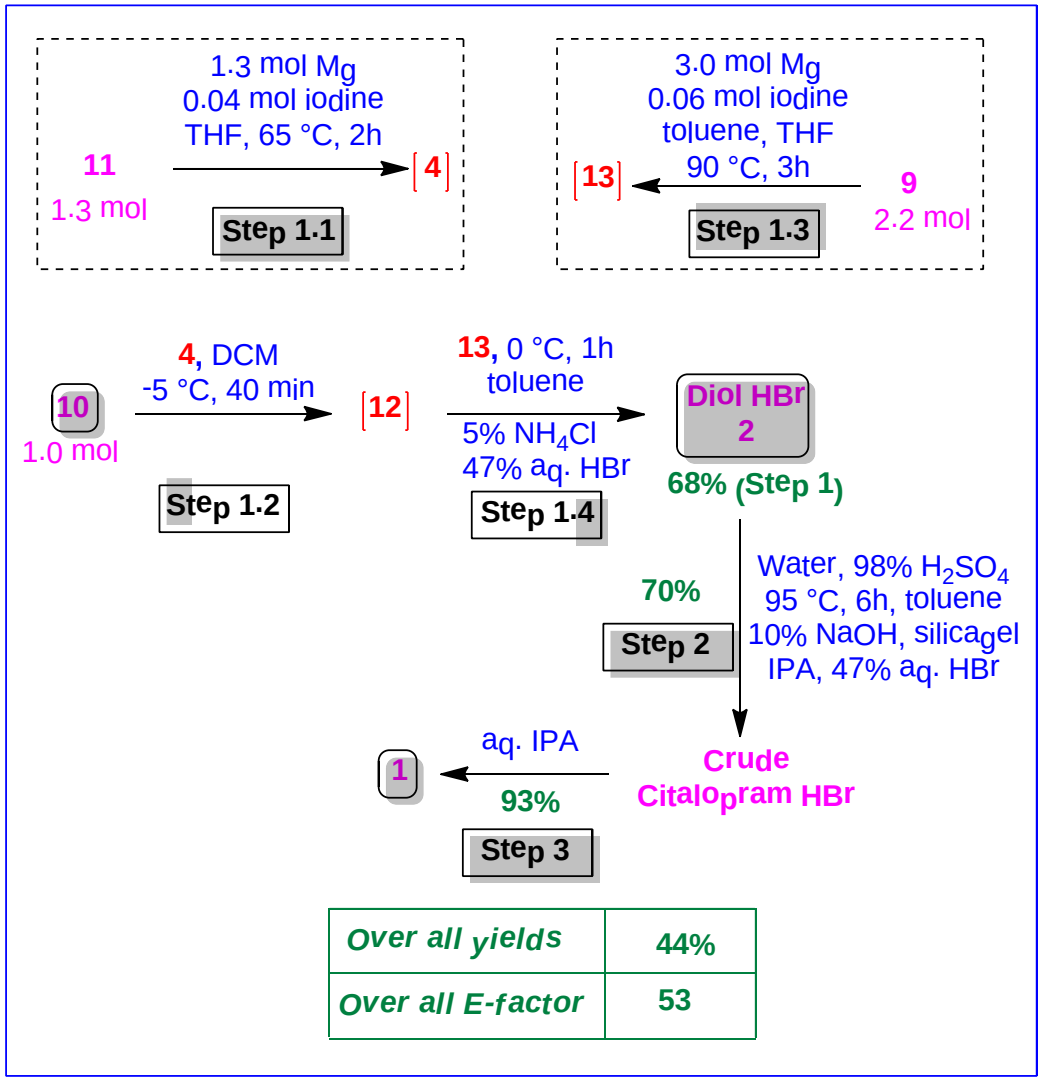
>75% yield and >98% purity

Design space obtained for BFB and CPA Grignard reactions





Optimized Conditions



Over all yields	44%
Over all E-factor	53

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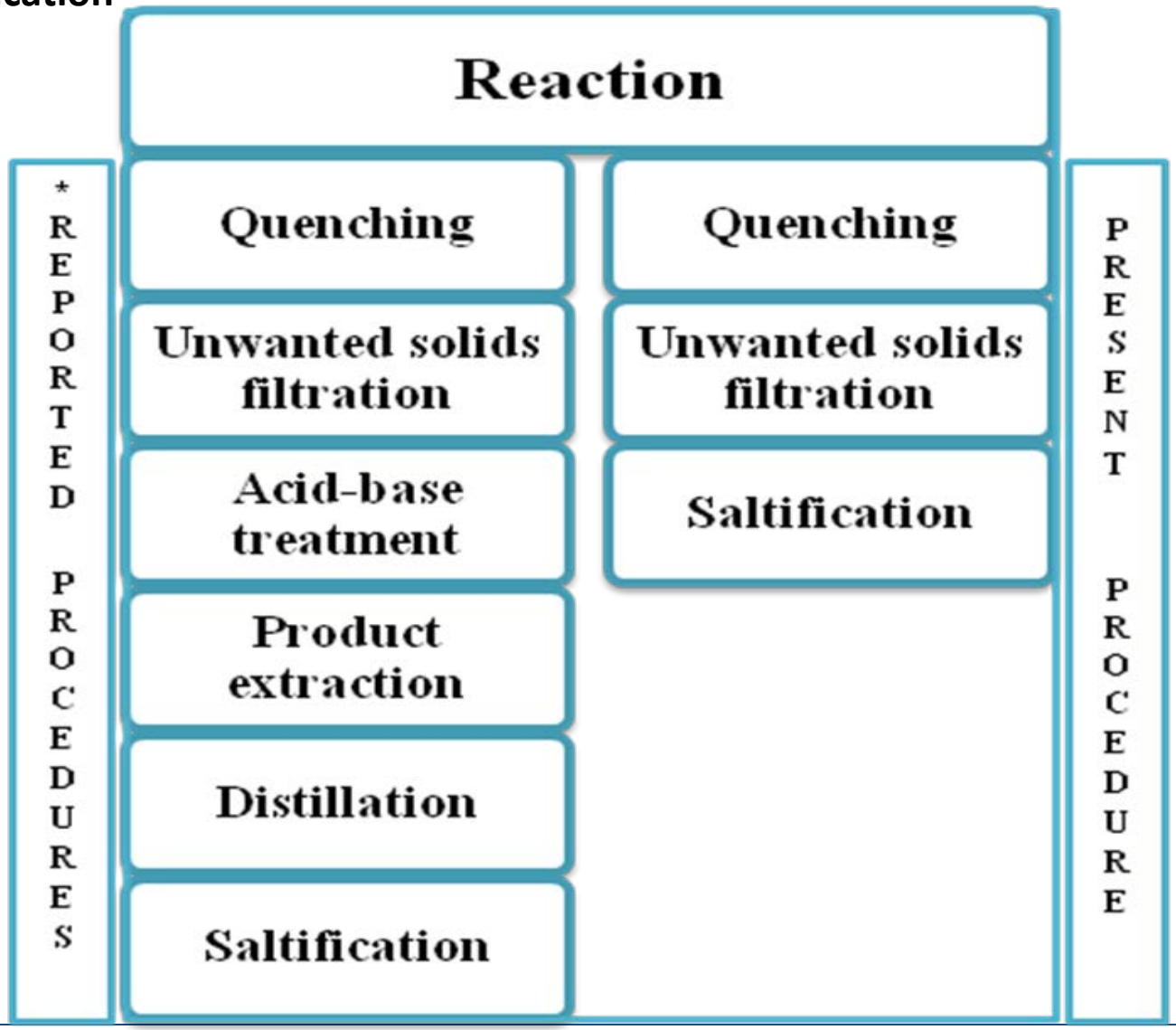
Work up Simplification



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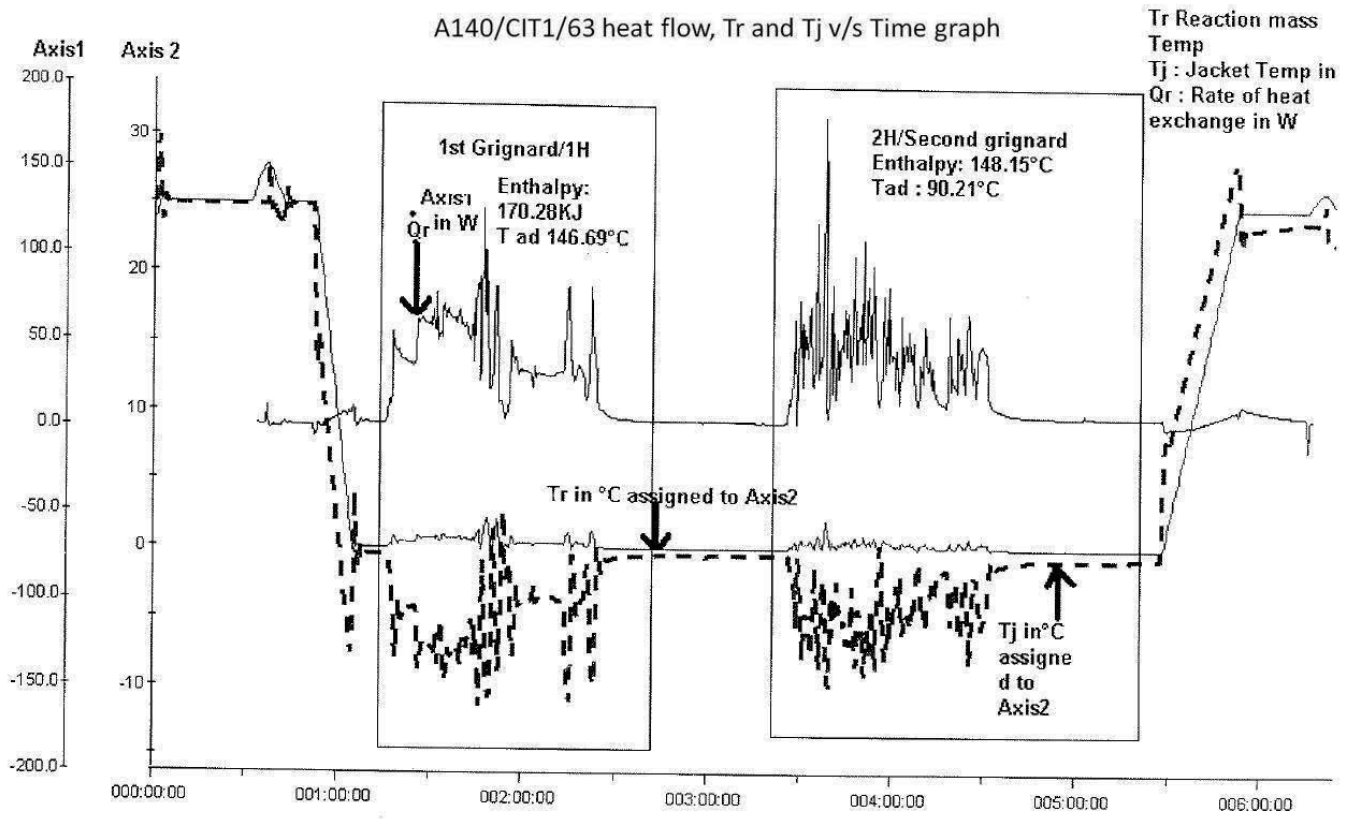
Safety Consideration

1. Understanding the heat of reaction and adiabatic temperature rise
2. Comparison of the batch temperature profile inside the reactor (Tr) with the reactor jacket temperature profile (Tj) in isothermal mode reveals whether the reaction is instantaneous or not. (Exo or Endothermic)
3. Enthalpy can be calculated which indicates temperature rise in a given batch size
4. This helps to avoid accidents at a scale by keeping control system in place without compromising on process variables and responses

Safety Consideration



For 100g input of **10**; Temperature rise for BFB Grignard is from 0 °C to 3 °C, E=170.2 KJ and Tad=146.69 °C; Temperature rise for CPA Grignard is from 0 °C to 1.5 °C, E=148.15 KJ and Tad=91.2 °C. Recommendation: Rate of heat exchange must be controlled by keeping efficient cooling in Jacket

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Appreciation

Michael E Kopach <kopach_michael@lilly.com>
05/10/2013 04:45 AM
To
"rakeshwarb@drreddys.com" <rakeshwarb@drreddys.com>

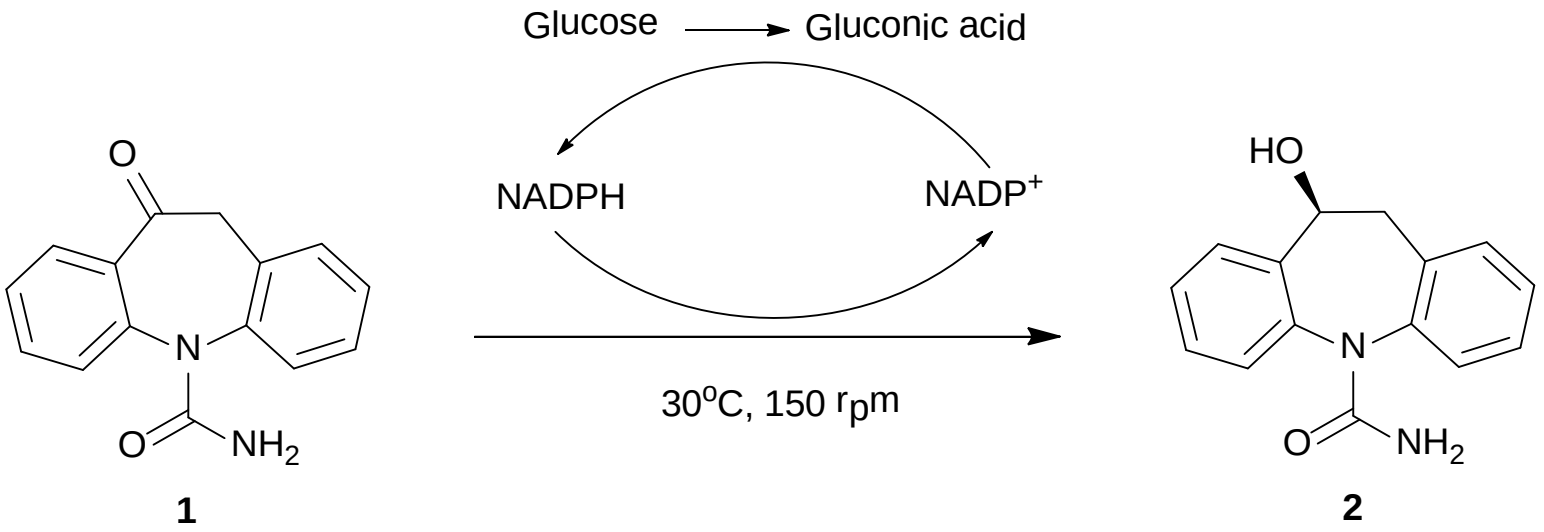
Cc
Subject
Citalopram Paper
Dear Rakesh,
From on Grignard practioner to another – this is an outstanding paper:
http://pubs.acs.org/doi/abs/10.1021/op3002596

Best Regards,

Mike

Org.Proc.Res.&Dev. **2013**, *17*, 798-805.

Asymmetric Reduction of a Key Intermediate of Esclicarbazepine Acetate Using Whole Cell



1

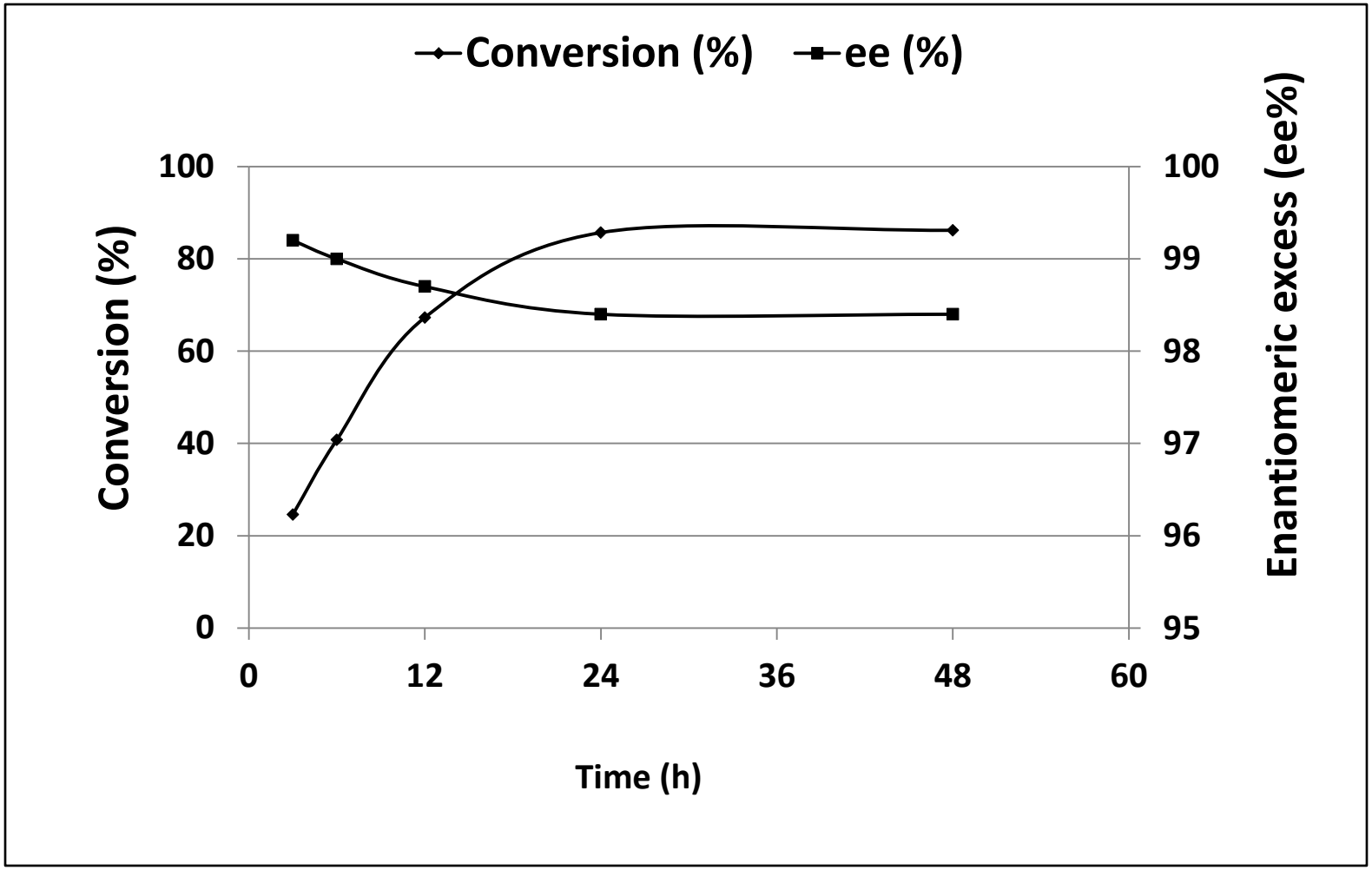
10-oxo-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

2

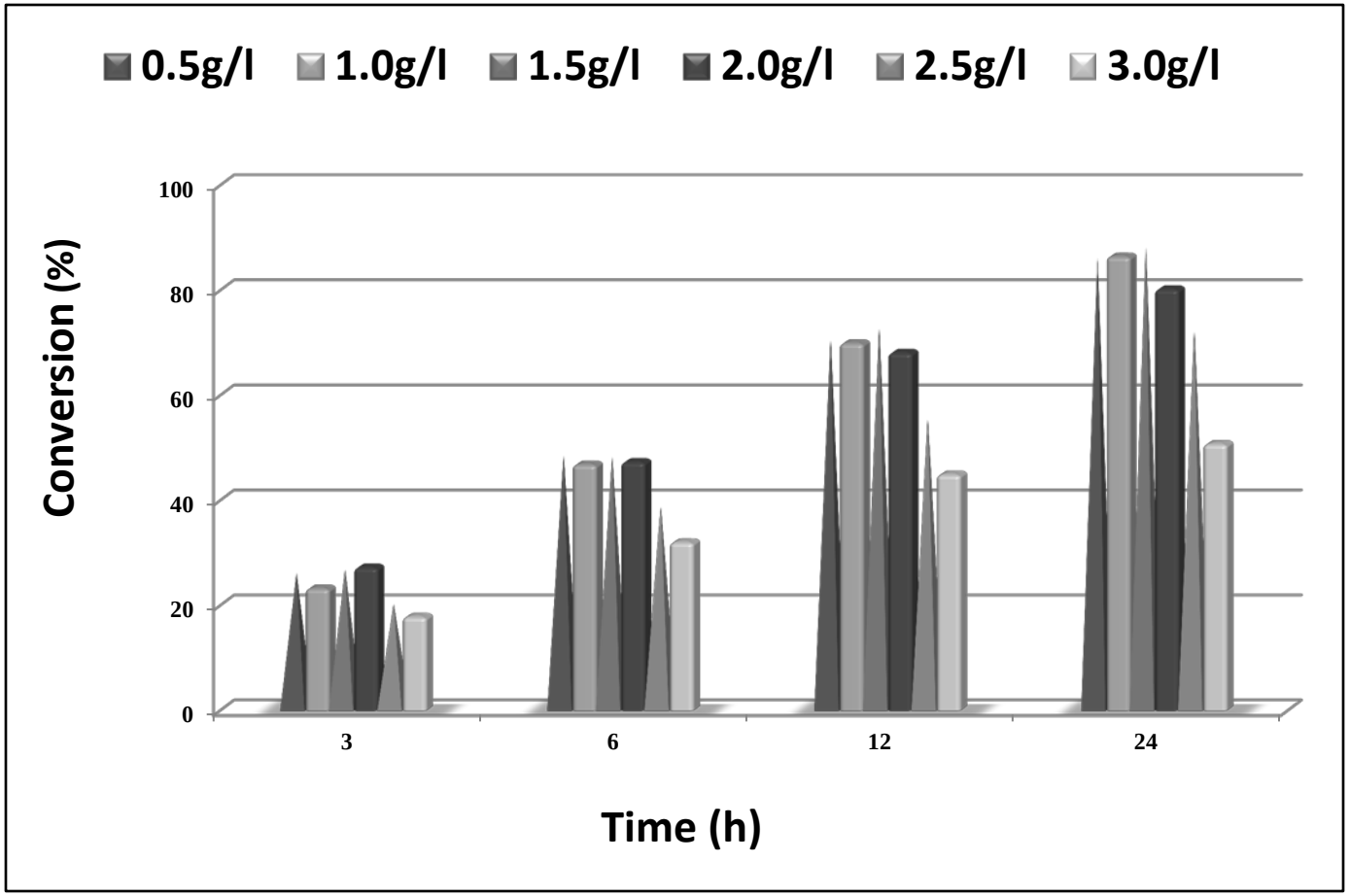
(*S*)-10-hydroxy-10,11-dihydro-5*H*-dibenzo[*b*,*f*]azepine-5-carboxamide

Catalysis Science & Technology **2012**, *2*, 1602-1605. (***One of the Hot Articles***).

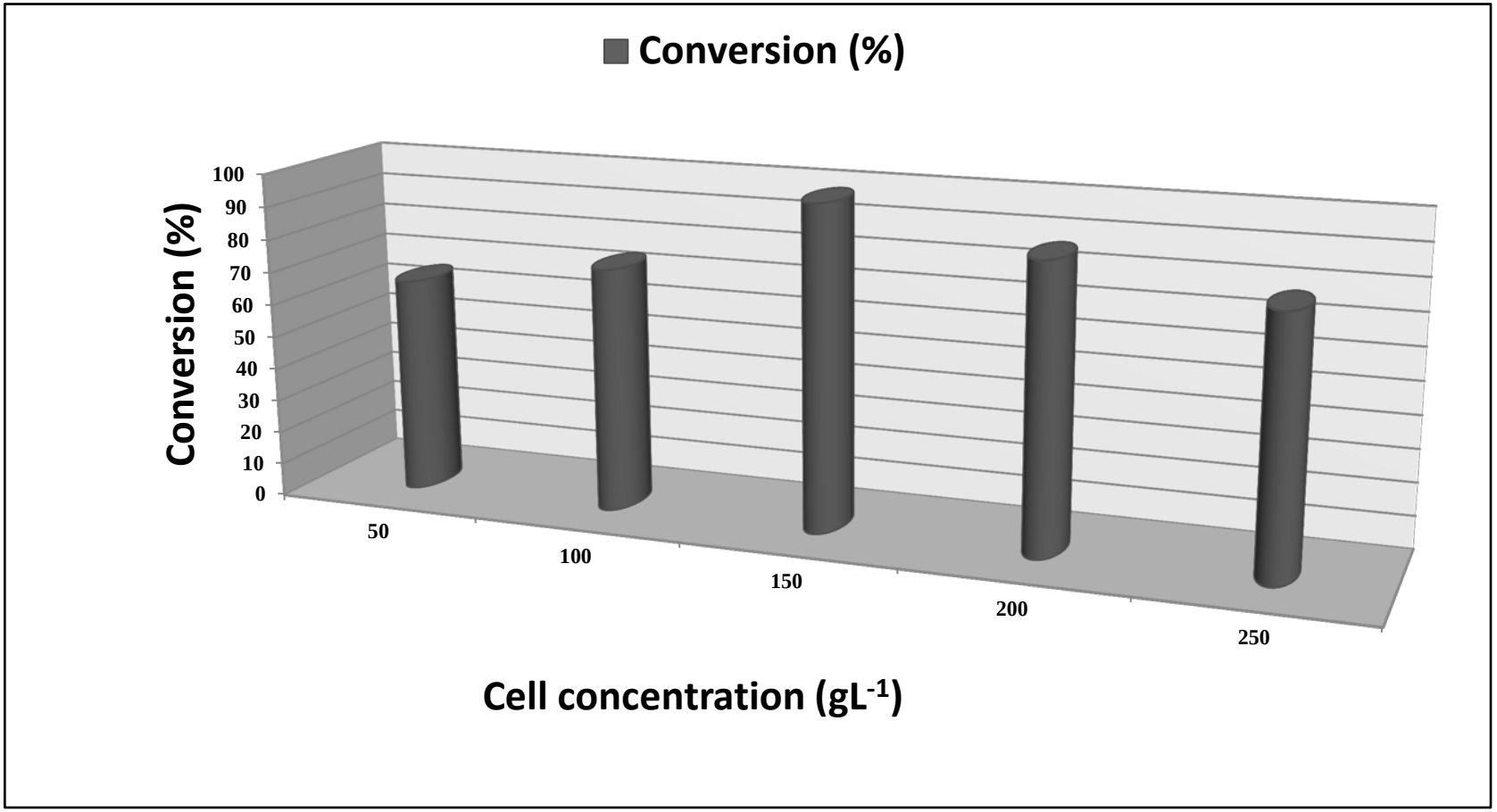
Bioreduction of Ketone 1 by *P. methanolica* whole-cells in biphasic system at 30°C



Effect of Substrate Concentration



Effect of Cell Concentration



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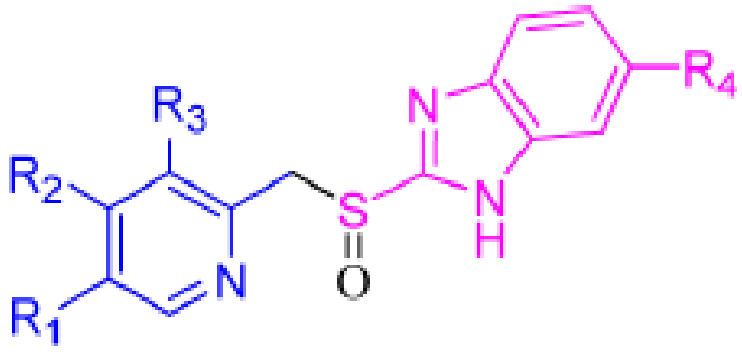
Output at a Scale with Optimized Conditions

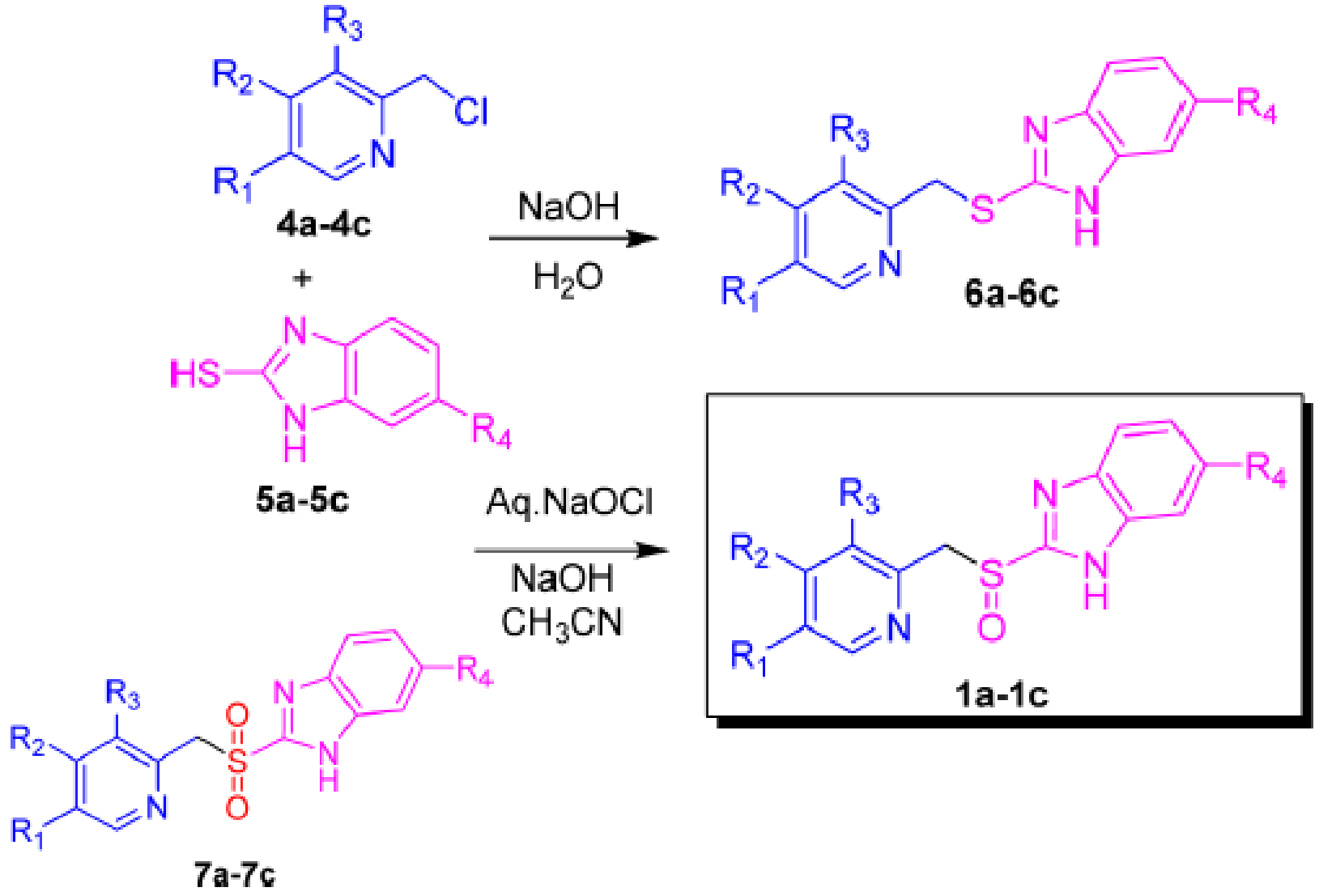
1. Resting cells of *P. methanolica* (150.0 gl^{-1}), H_2O: hexane (2 L), glucose (0.5%)
2. Reaction at 30 °C for 48 h
3. 85% isolated with >98% *ee*

Application of Flow Technology in the Process Development of Prazoles

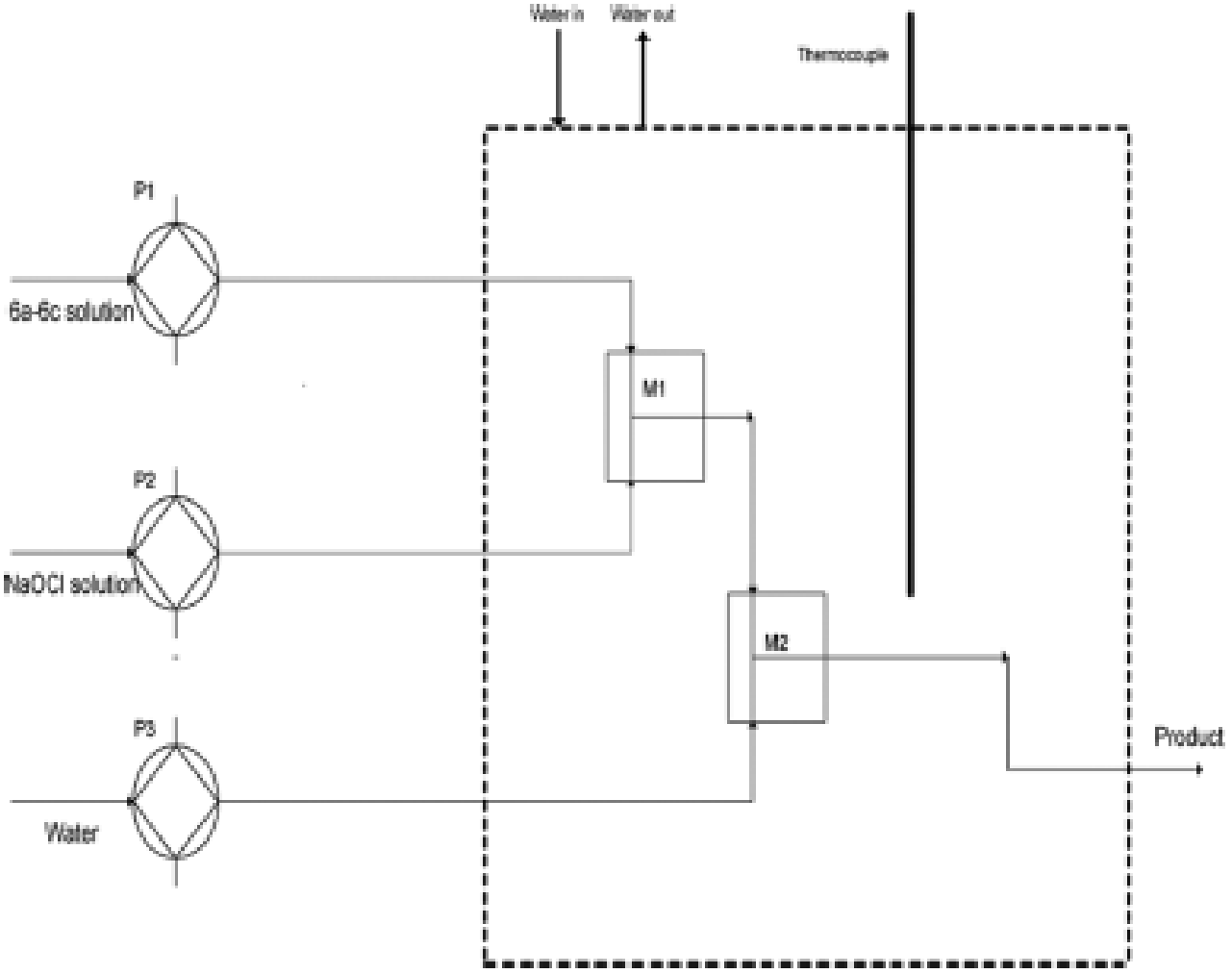


	Drug name	R1	R2	R3	R4
1a	Lansoprazole	-H	F_3CCH_2O-	Me	-H
1b	Pantaprazole	-H	MeO	MeO	F_2CHO-
1c	Raberprazole	Me	MeO $(CH_2)_3O$	Me	-H

Synthesis of Prazoles



Continuous Flow Micromixing Reactor Set up



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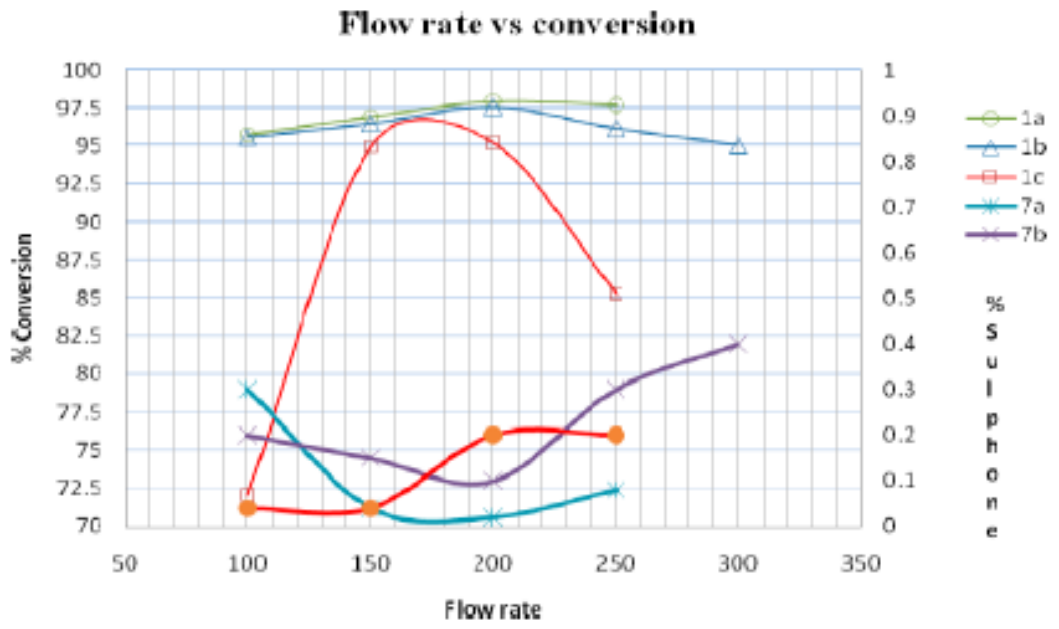
Effect of Flow Rate on Conversion

entry	flow rate (mL/min)	reaction mass HPLC purity (%)		
		6a	1a	7a
1	100	0.95	95.72	0.30
2	150	0.75	96.92	0.04
3	**200**	**0.30**	**97.94**	**0.02**
4	250	0.70	97.70	0.08



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Batch vs Flow

entry	oxid'n of 6	synthesis method	residence time
1	6a	batch process	2.5 h
2	6b		2.5 h
3	6c		2.5 h
4	6a	CFMMR[a]	~1 s
5	6b		~1 s
6	6c		~1 s

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Batch vs Flow

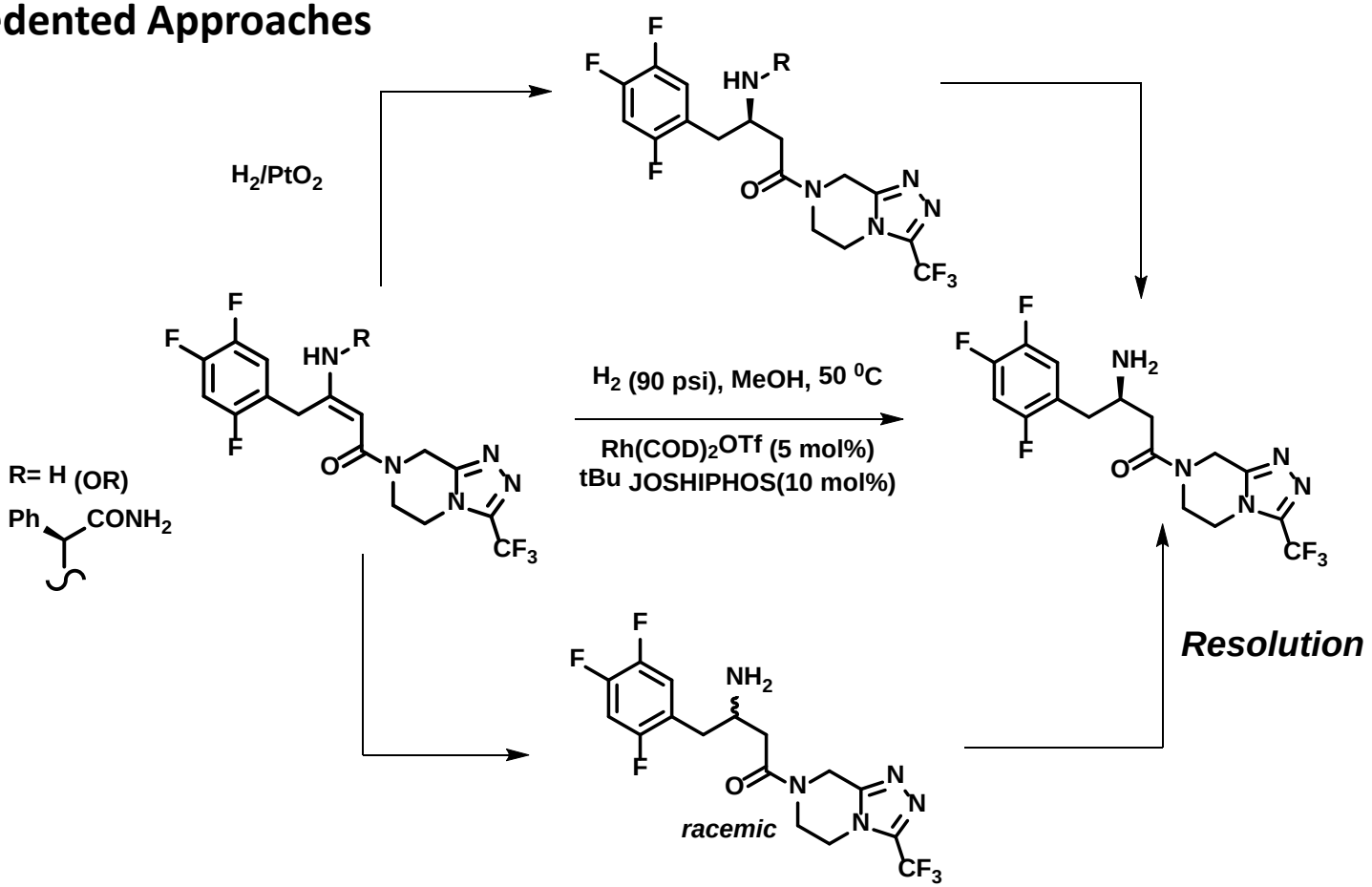
before purification			after purification			
	purity (%)		purity (%)			
yield (%)	1a–1c	7a–7c	1a–1c	7a–7c	yield (%)	overall yield (%)
85.0	97.5	0.13	99.6	0.18	74.0	62.9
92.9	97.2	0.05	99.7	0.08	86.0	79.8
85.0	98.2	0.08	99.5	0.05	78.2	66.5
89.0	96.5	–	99.9	0.06	79.4	71.0
94.8	97.9	–	99.5	0.07	89.8	85.1
88.2	98.7	0.10	99.5	0.03	85.1	75.0

First three entries are from Batch and last three belong to Flow

Org. Process Res. Dev., **2010**, *14*, 229–233 (DRL, India)
Org. Process Res. Dev., **2013**, *17*, 1272–1276 (DRL, India)

Major Innovation: Diastereoselective Reduction

Precedented Approaches



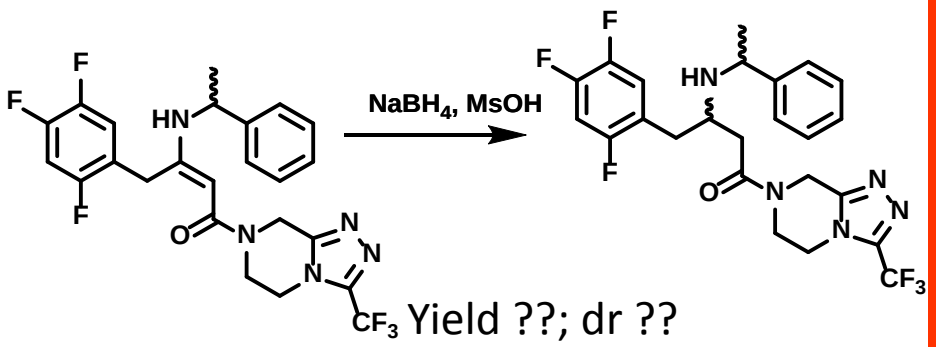
Recently Developed Asymmetric Reduction Involving Biocatalysis is More Prefered

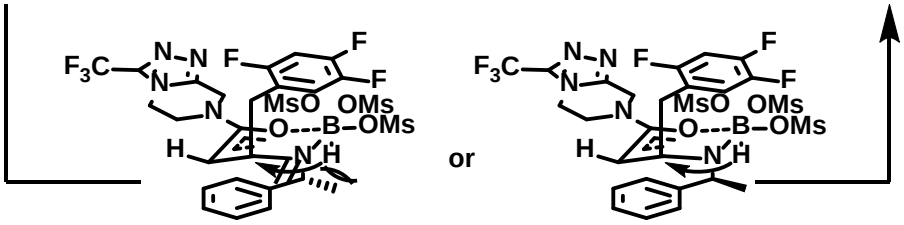
Hansen, K.B.; Hsiao, Y.; Xu, F.; Rivera, N.; Clausen, A.; Kubryk, M.; Krska, S.; Rosner, T.; Simmons, B.; Balsells, J.; Ikemoto, N.; Sun, Y.; Spindler, F.; Malan, C.; Grabowski, E.J.J.; Armstrong III, J.D. *J. Am. Chem. Soc.* 2009, *131*, 8798-8804

Major Innovation: Diastereoselective Reduction

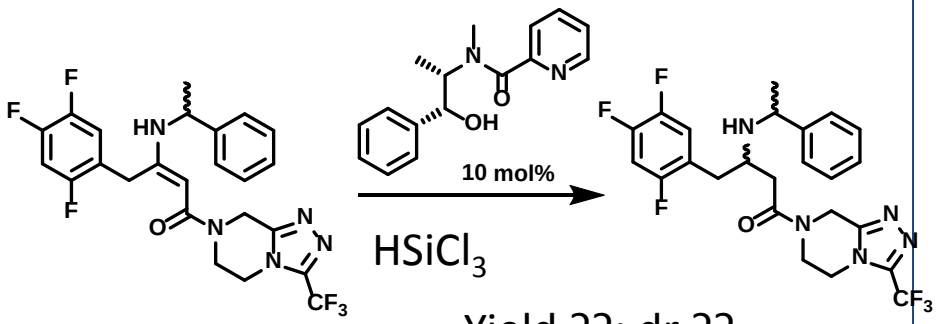
Innovative Approaches

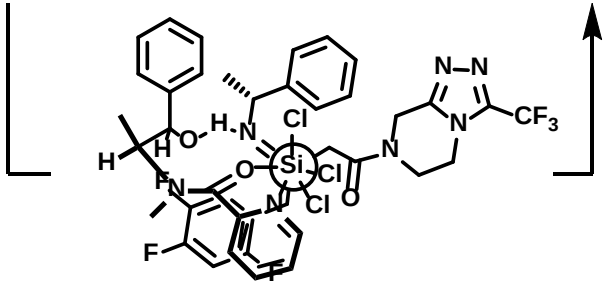
Strategy I





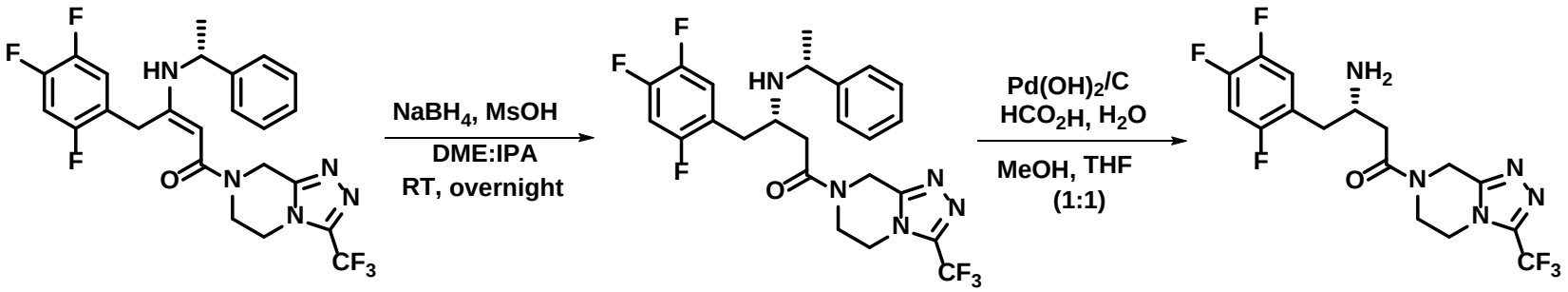
Strategy II



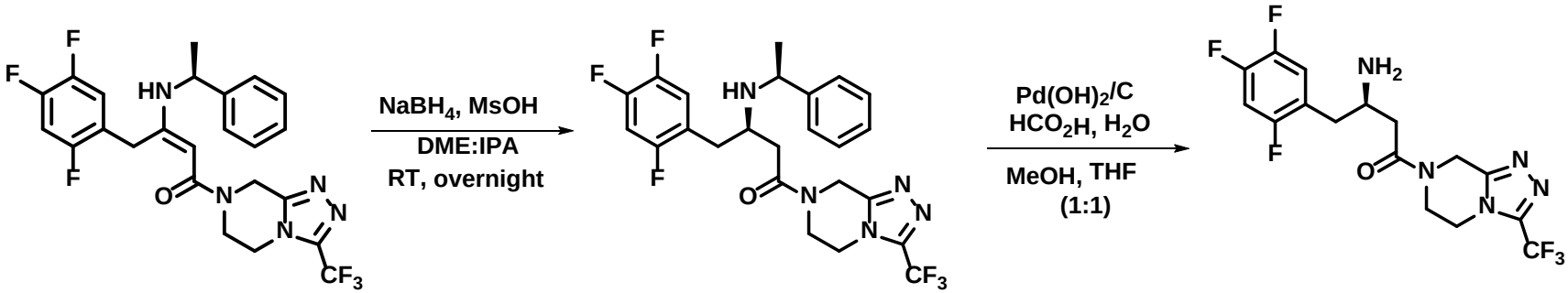


Major Innovation: Diastereoselective Reduction

Evolution of Concept

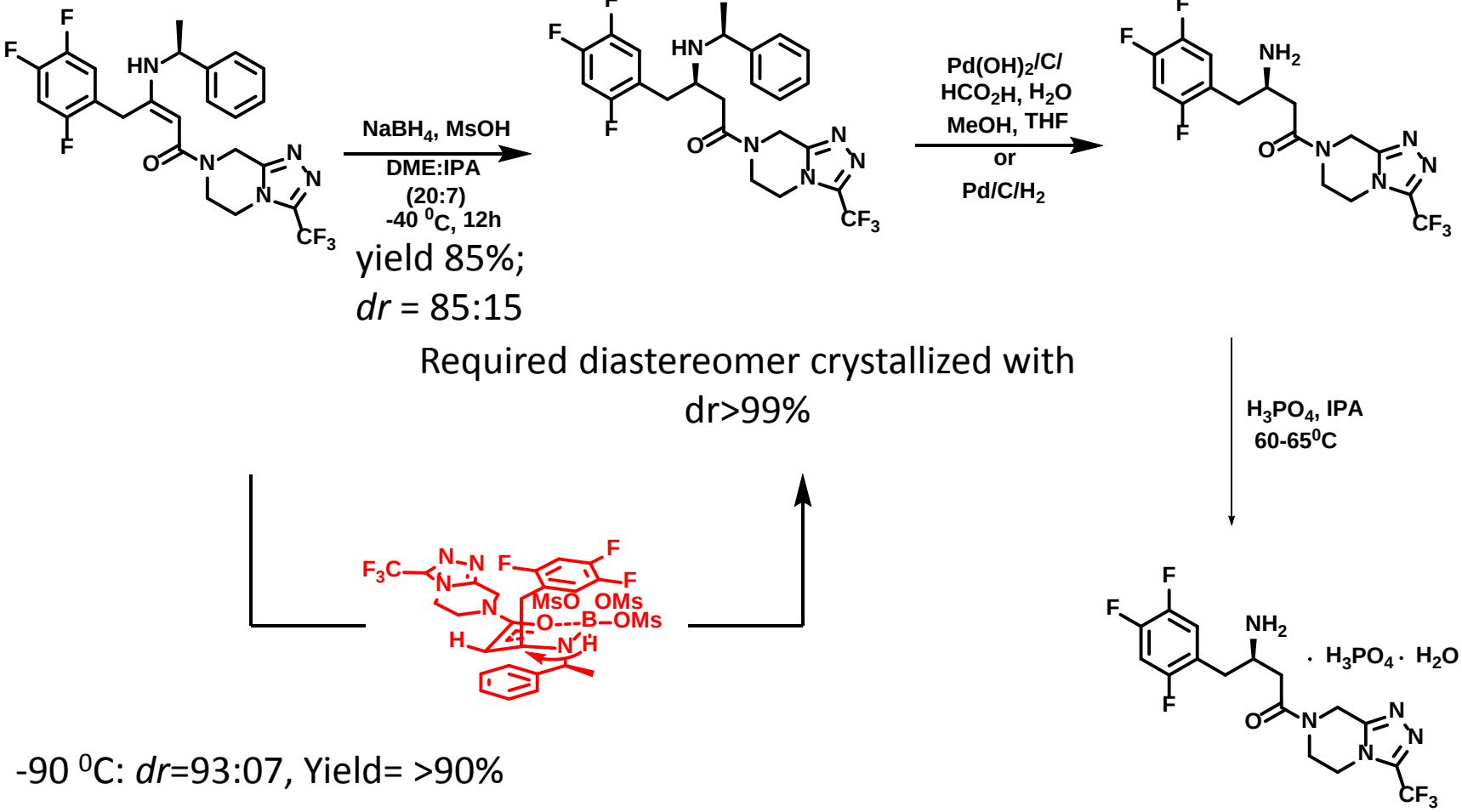


dr : 83:17
undesired isomer



dr: 85:15
desired isomer

Major Innovation: Diastereoselective Reduction



-90 ^{0}C: *dr*=93:07, Yield= >90%

7000 *vs* 700 USD

Bandichhor, R.; et al. WO 2011025932 A2 20110303

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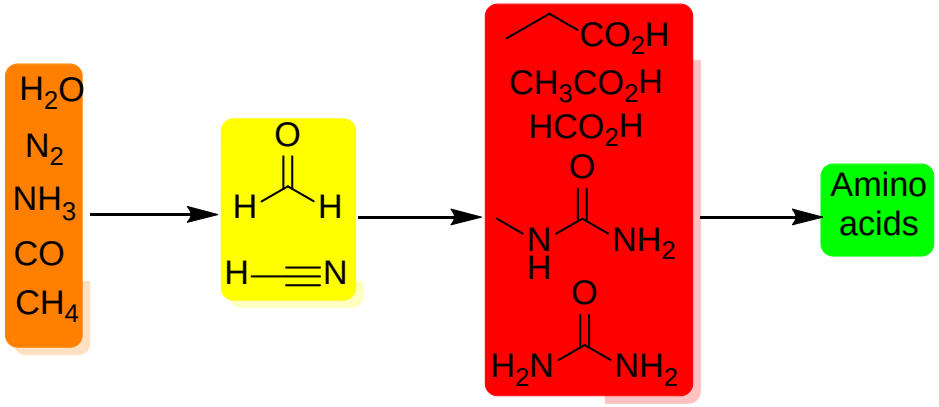
Discovery of Redox System Enabling C-N-C Bonds Formation: Indicator of Prebiotic Synthesis of Amino Acid

Miller-Urey



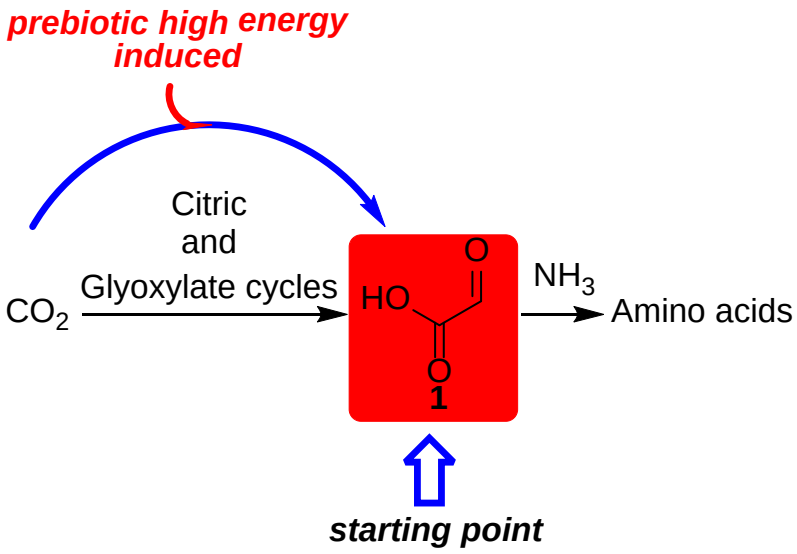
Calvin

$CO_2 \longrightarrow HCO_2H \longrightarrow$ Amino acids

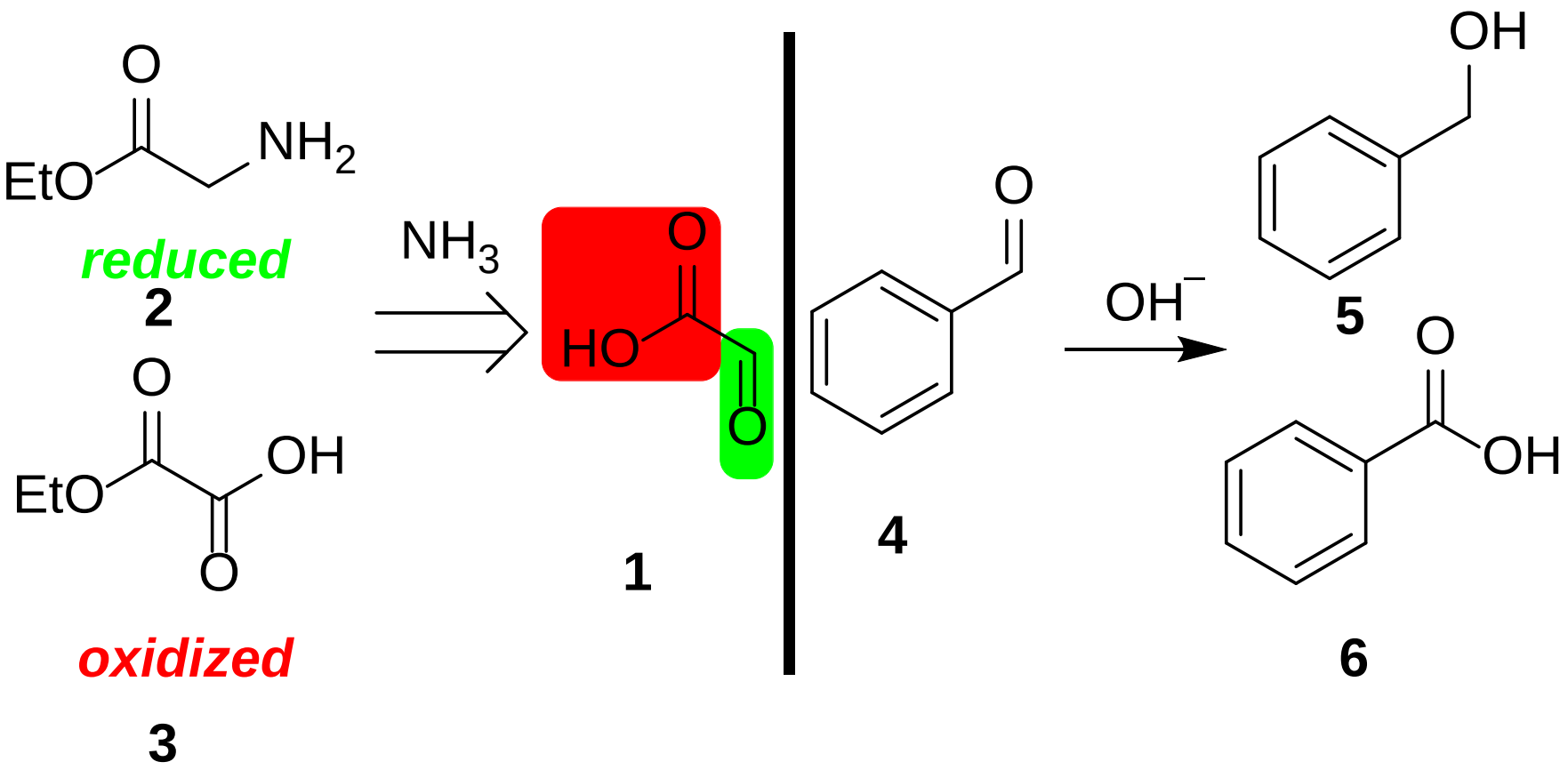
Karat

$HCN \xrightarrow{NH_3} \longrightarrow \longrightarrow$ Amino acids

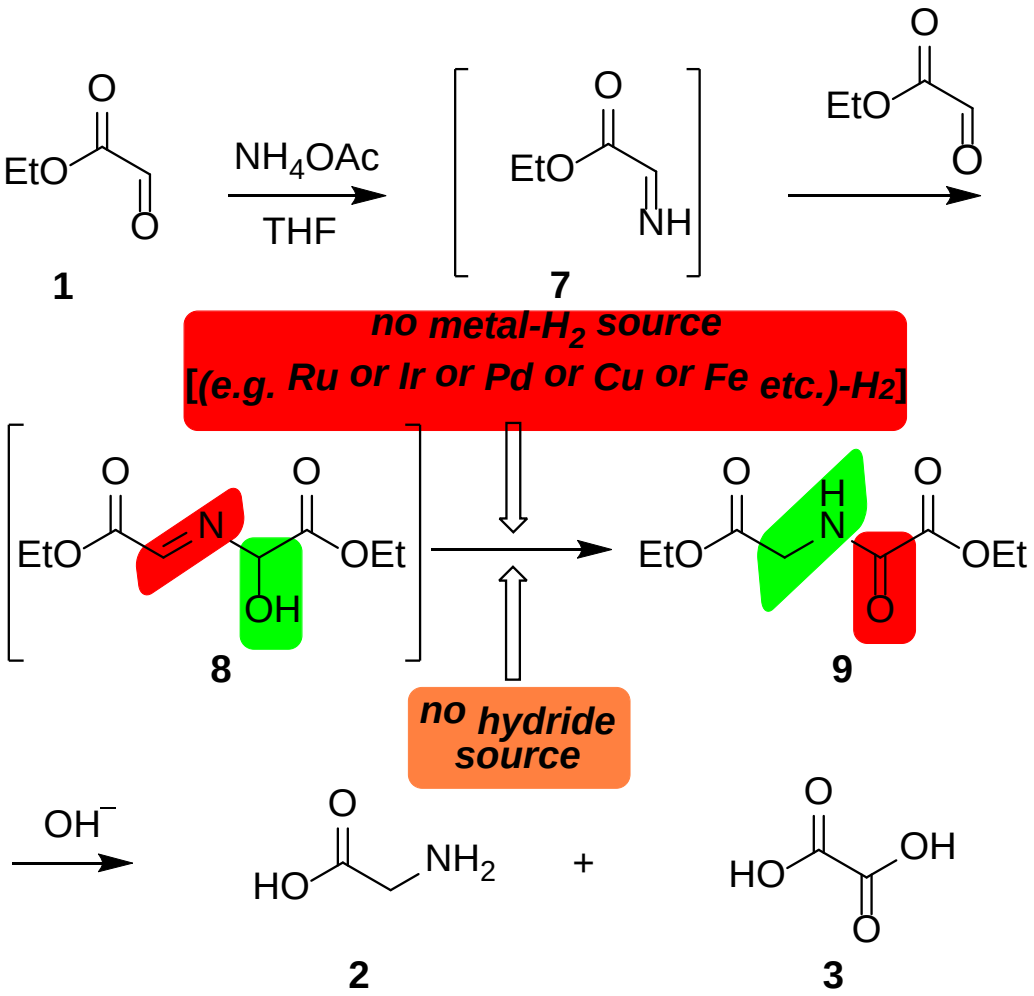
Our work



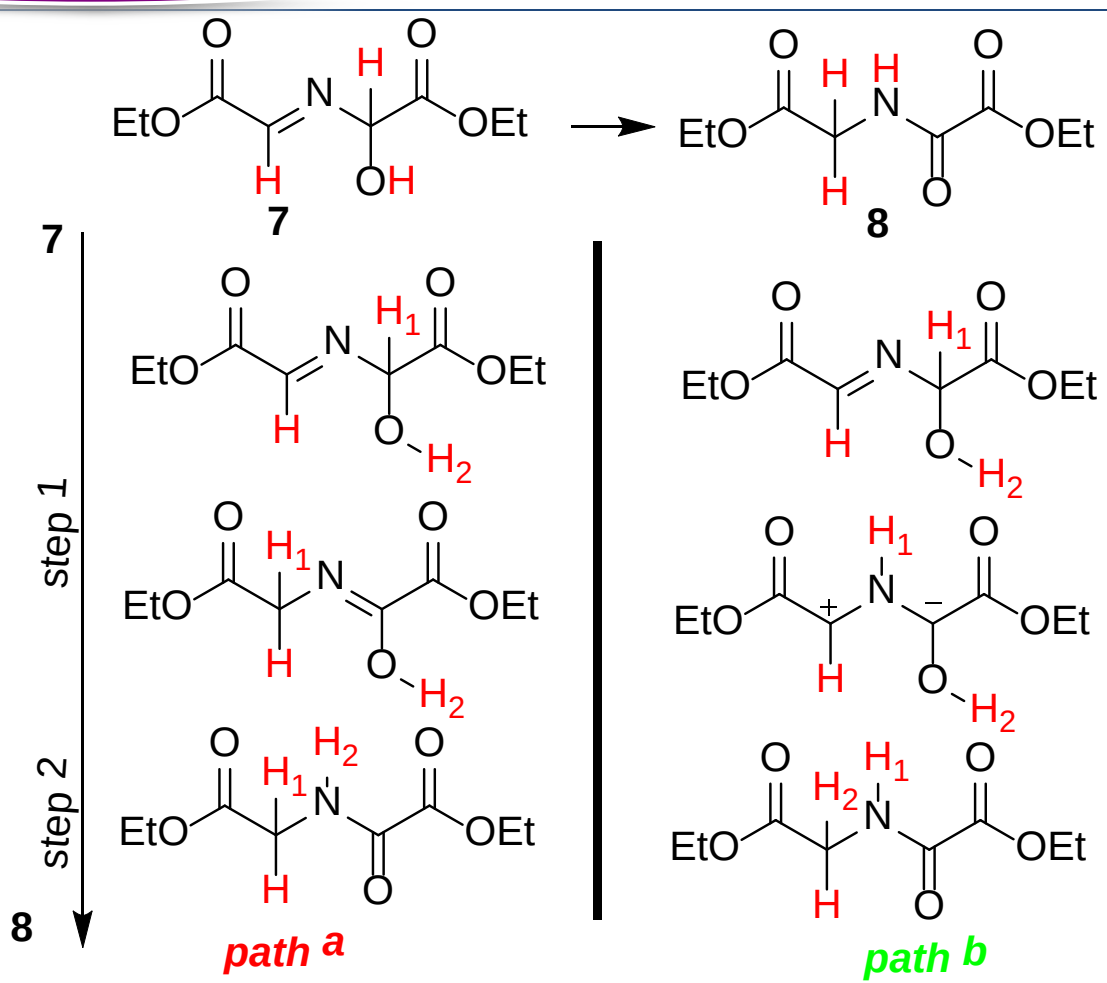
Different conceived approaches towards the synthesis of amino acids



Redox chemistry on ethyl glyoxylate and Cannizzaro reaction

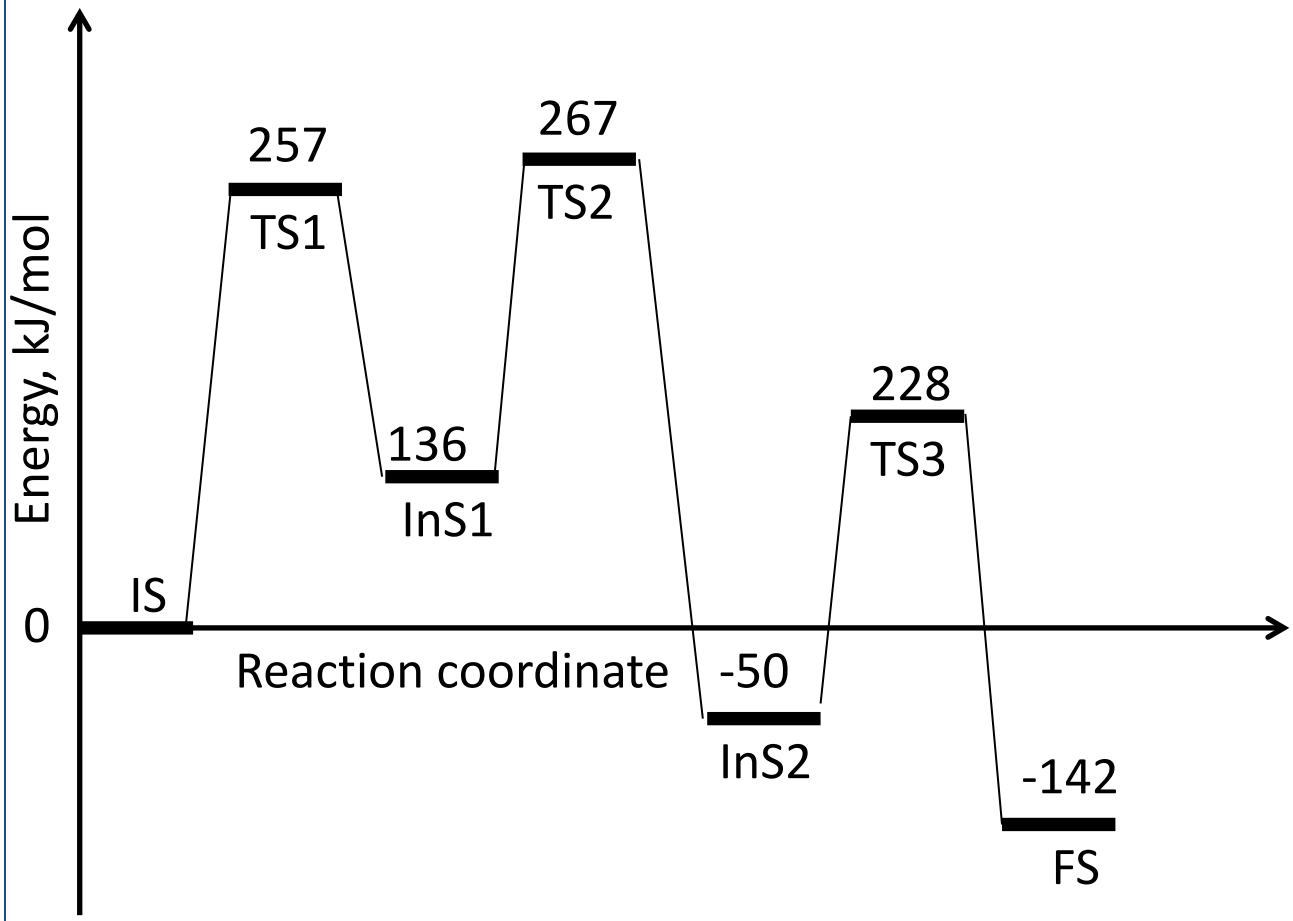


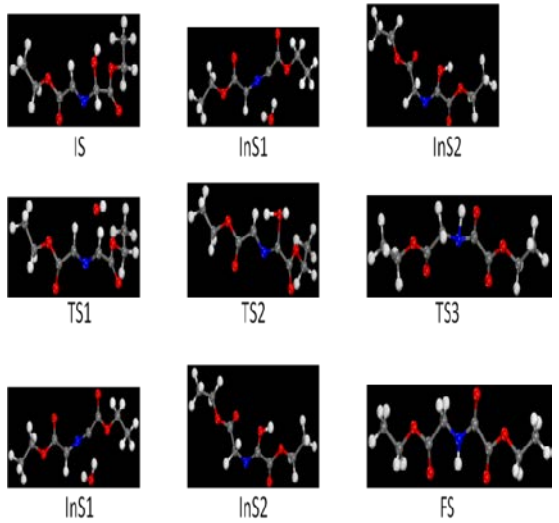
Synthesis of glycine **2**



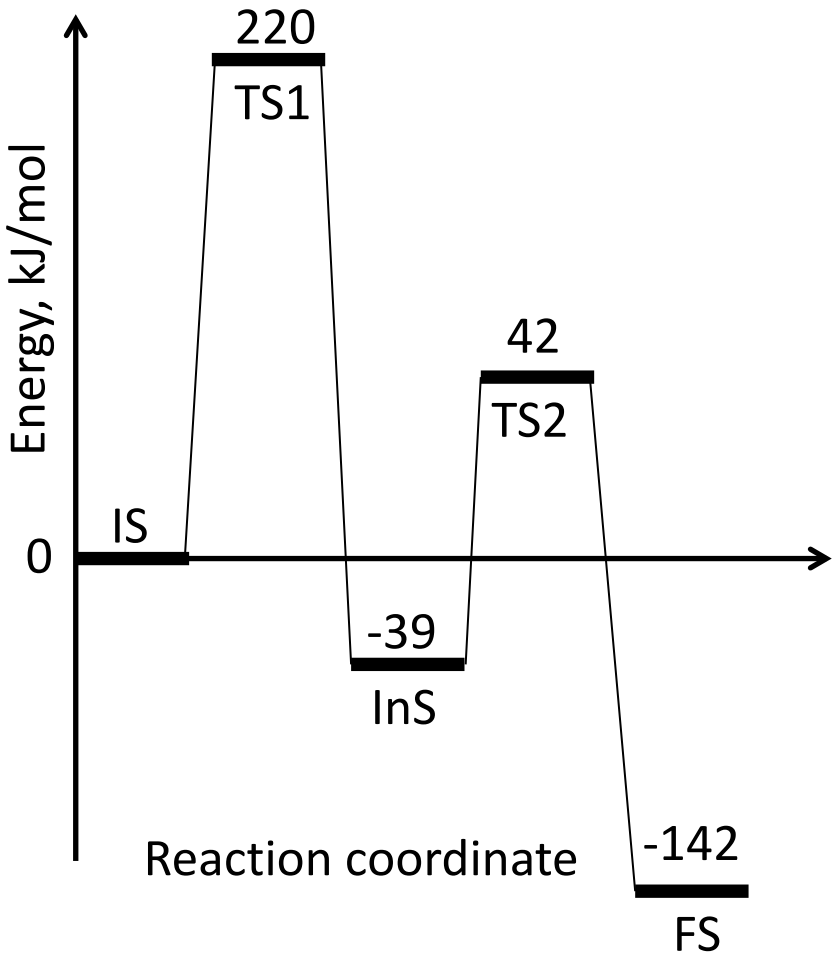
Two different reaction pathways (**a** and **b**)

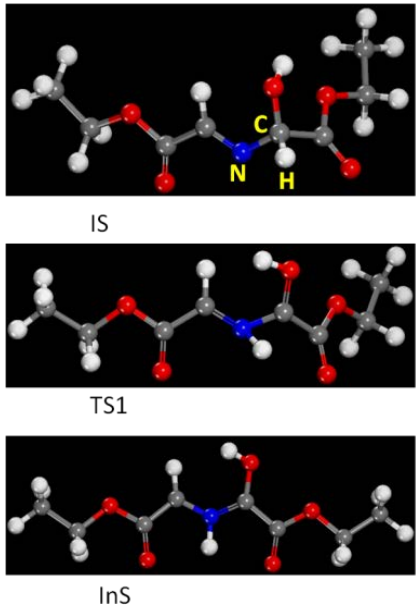
Major Innovation: Amino Acid

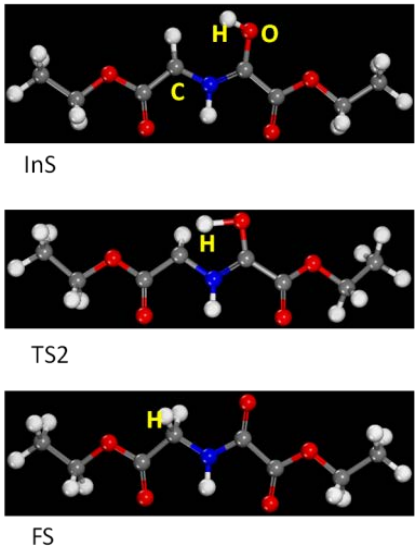




Major Innovation: Amino Acid







Bandichhor et al. *Chem. Com.* **2014** under revision

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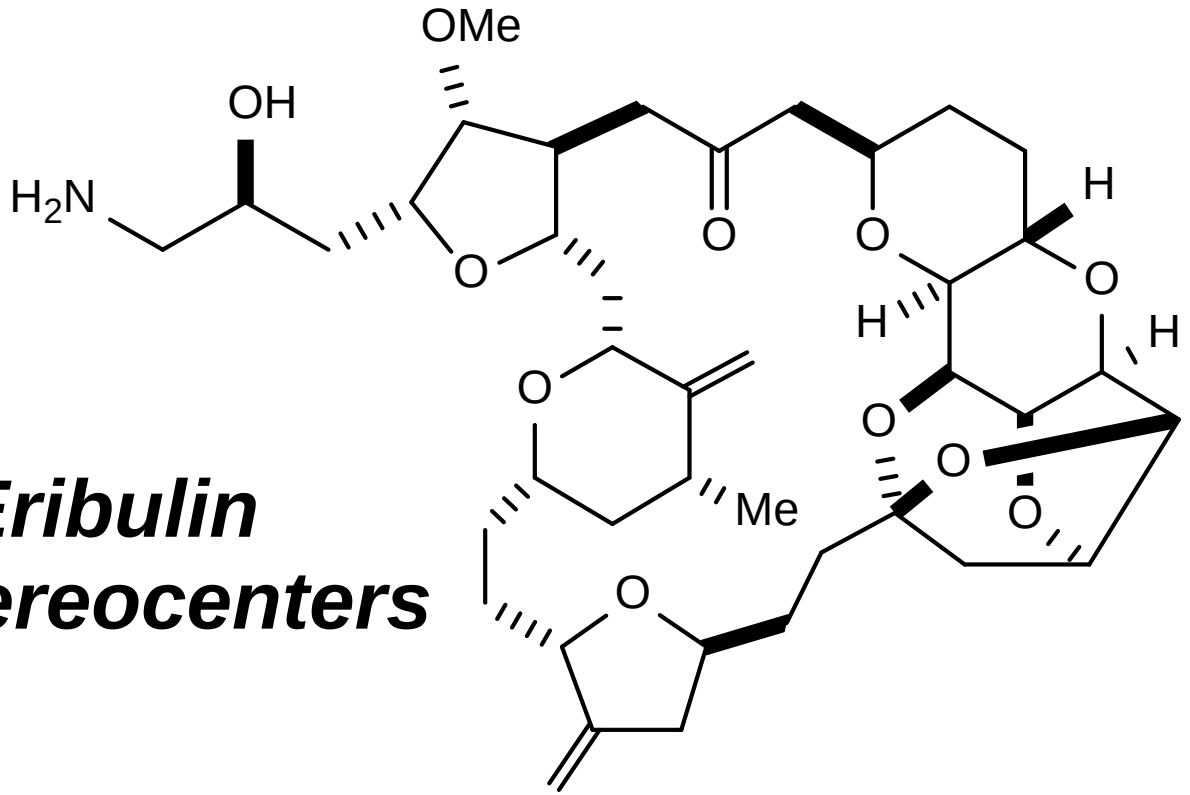
Target 64 to 20 Steps

HALAVEN is a clear, colorless, sterile solution for intravenous administration. Each vial contains 1 mg of eribulin mesylate as a 0.5 mg/mL solution in ethanol: water (5:95).

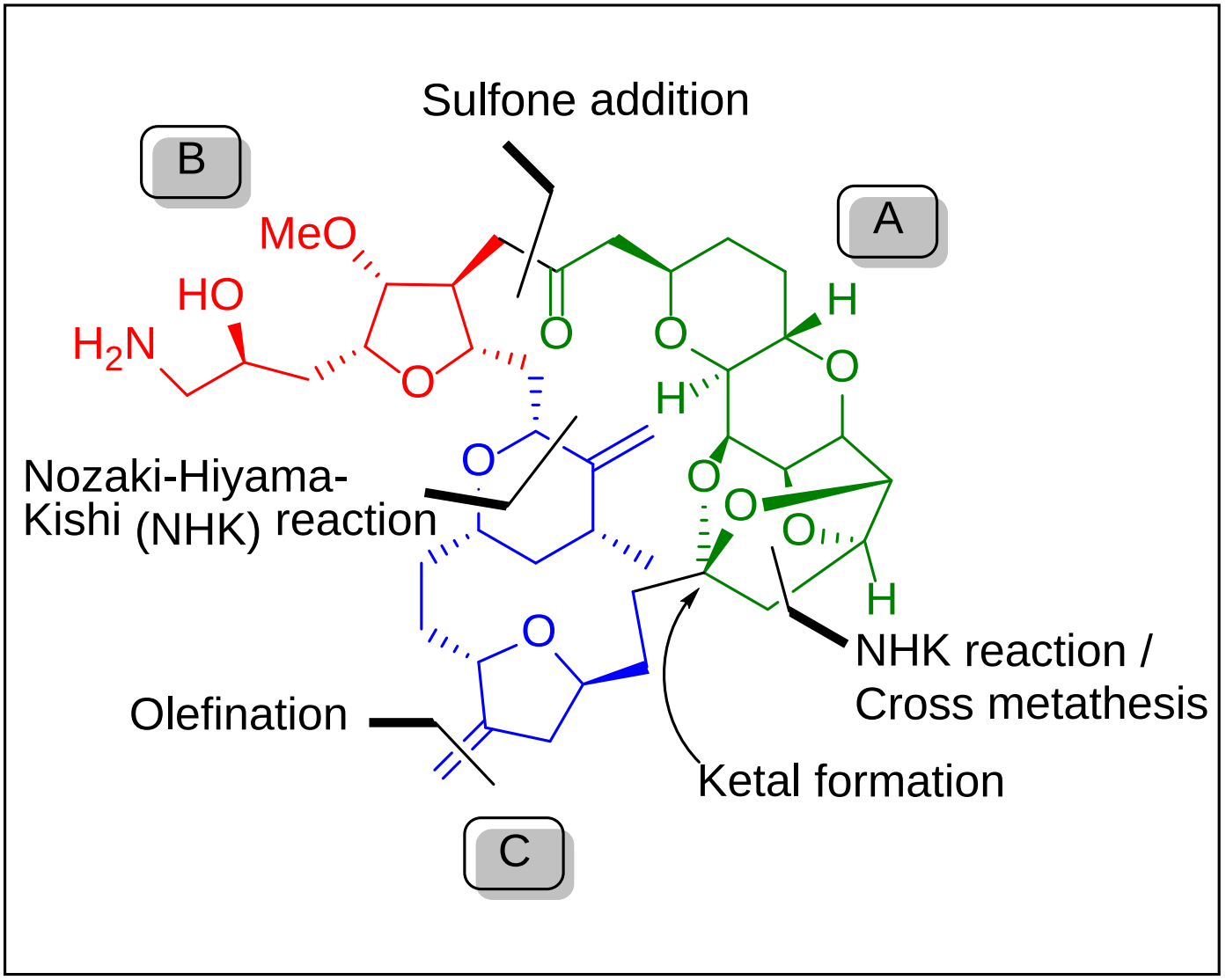


Eribulin

19 stereocenters

Late Stage Breast Cancer (Two Chemotherapies and Treated With Anthramycin and Taxane Class of Medicine)

Major Innovation: Synthesis of Eribulin



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"A chain is as strong as its weakest link"

Reading Materials:

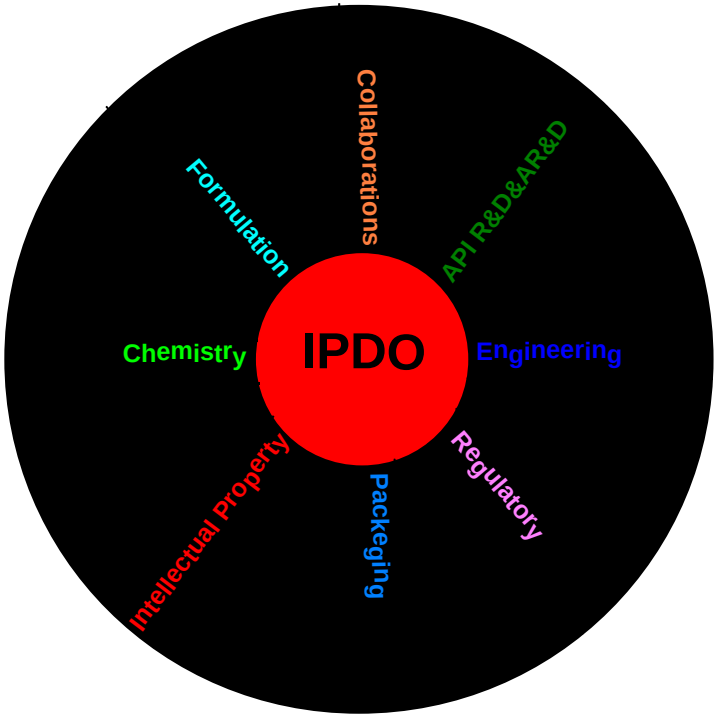
1. Scalable Green Chemistry: Case Studies from the Pharmaceutical Industry
2. Green Chemistry in the Pharmaceutical Industry

Apart from Leading Journals

1. OPRD
2. Journal of Chemical Education

Green Innovation Award-2013 in the Large MNC Category

Acknowledgement



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Thank You