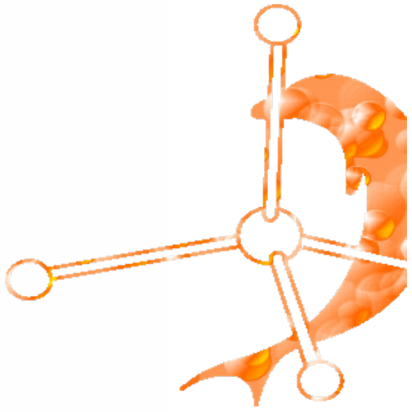
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IMPACT OF NEW SYNTHETIC METHODS ON DRUG DISCOVERY

ABCD

New Synthetic Method: Any reaction or synthetic protocol discovered in the last 30 years.

What kind of synthetic methodology is used nowadays in the practice of mainstream Medicinal Chemistry?

Is there a synergy between the new synthetic methodologies described nowadays in academic labs and the drug discovery business? Is the new chemistry being translated into practical results?

IMPACT OF NEW SYNTHETIC METHODS ON DRUG DISCOVERY

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Type of molecule	J. Med. Chem.	Bioorg. M.C.L.	Comment
No synthesis in paper	10 (40%)	7 (15%)	Database mining, docking, QSAR
Flat	7 (28%)	21 (47%)	
With stereochemistry	8 (32%)	17 (38%)	
Total	25	45	
Ster. from Chiral pool	4	13	
Use of racemates	2	3	
Ster. by resolution	1	-	
Diastereoselective Synthesis	**-**	**1**	**F. Davis oxaziridine**
Enantioselective Cat.	**1**	**-**	**Sharpless ADH**

A recent 2004 issue of *J. Med. Chem*. analyzed (25 papers).
For comparison, also recent issue of *Bioorg. Med. Chem. Lett*. analyzed (45 papers).

REACTIONS USED

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Reaction type	% Occurrence in J.Med. Chem.	% Occurrence in Bioorg. M.C.L.	Comments
Protect./Deprot.	21.9	21.8	
Acylations	13.9	21.1	Amide, ester, urea
Subst. at sp^3 C	12.1	12.9	Ethers, amines
Condensations	9.2	4.0	Aldol, malonate
Reductions	6.4	10.9	H_2, hydrides etc
Oxidations	6.4	7.3	
SN Ar	4.6	5.9	
Cross-coupling	4.6	3.3	Pd-cat. C-C, C-N
Red. Amination	4.0	2.0	
N, O sulfonation	4.0	1.0	
Addition to C=O	2.9	2.3	Tebbe (1 example)

REACTIONS USED (cont.)

ABCD

Reaction type	% Occurrence in J.Med. Chem.	% Occurrence in Bioorg. M.C.L.	Comments
Hydrolysis	2.3	0.7	Nitriles
El. Arom. Subst.	2.3	1.0	F.C., nitration
Ring Lith.	2.3	0.3	
N, O Phosph.	1.1	1.3	
Mitsunobu	1.1	0.3	Esters (1968)
Cycloadditions	0.6	0.7	D.A., [2+3]
Conjugate Additions	0.6	1.0	To enones, uns. esters
Imine/Oxime form.	0.3	2.0	
Dihydroxylation	0	0.3	Sharpless
Enolate hydroxyln	0	0.3	Oxaziridine

TENTATIVE CONCLUSIONS

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• Of all synthetic steps used, 35-40% are steps that do not achieve molecular construction (*i.e*. blocking, deblocking and oxidation state adjustments). *Synthetic efficiency is clearly of little concern to Medicinal Chemists.*

• Only 15-20% of all steps involve C-C bond formation. The majority involve C-N and C-O bond formation.

• Cycloadditions, cascade reactions, and multicomponent condensation methods are conspicuously absent from the toolbox of the Medicinal Chemist.

• Only 3.9-5.7% of the steps used comprise synthetic methods developed in the last 30 years. Of these, the cross-coupling reaction (C-C, C-N coupling) is the only tool systematically used by the Medicinal Chemist.

FURTHER COMMENTS / IMPRESSIONS

ABCD

- Application of organic synthesis in discovery chemistry has not progressed but regressed in the last 10-15 years. This is probably due to:

- The emphasis on numbers of compounds (HTS).
- The rise of combinatorial chemistry and the need for easy, robust chemistry.
- The abundance of leads (no need to pursue the tough ones).
- The slow demise of natural products as leads.

- In general, most discovery compounds are still flat heterocycles with MW<500, <5 H bond donor moieties, <10 H bond acceptor moieties, optimal for **oral bioavailability** (Lipinski's rules). Therefore much of the methodology used in discovery is classical heterocyclic and aromatic chemistry, *i.e.* methods that were developed 50-150 years ago and never perfected.

- Unusual compounds, such as large natural products (modified or not), peptides, oligos, antisense and other difficult-to-deliver molecules that may require sophisticated synthetic methodology, will always play a role, but they are out of the current mainstream drug-discovery paradigms.

SYNTHETIC CHEMISTRY AND PROCESS CHEMISTRY

ABCD

Process Chemists focus on:

-Discovering the synthetically most efficient way to synthesize a given target.
-Developing the synthesis so it is convenient to carry out.
-Scaling it up in a manufacturing plant.

Academic Synthetic Chemists focus on:

-Developing new *general* methodology.
-Synthesizing targets of academic interest, if possible using new methodology.
-Finding new problems to which synthesis can be applied.

SYNTHETIC CHEMISTRY AND PROCESS CHEMISTRY

ABCD

Synthetic Chemists have little understanding of Process Chemistry.
Process Chemistry is NOT Synthetic Chemistry.

Food for thought

Since the chemical literature is run by academic chemists:

-A paper describing an efficient synthesis of a new drug in development does not get easily published.

-A paper describing an inefficient synthesis of a biologically unimportant natural product gets easily published.

A consequence: Organic Process Research and Development (ACS).

A STARTLING SUGGESTION

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"It is rather astonishing how little chemists really know about designing the shortest and simplest synthesis of a new molecule."
D. Bradley, *The New Scientist*, **1997**, *Nov. 15*, 40.

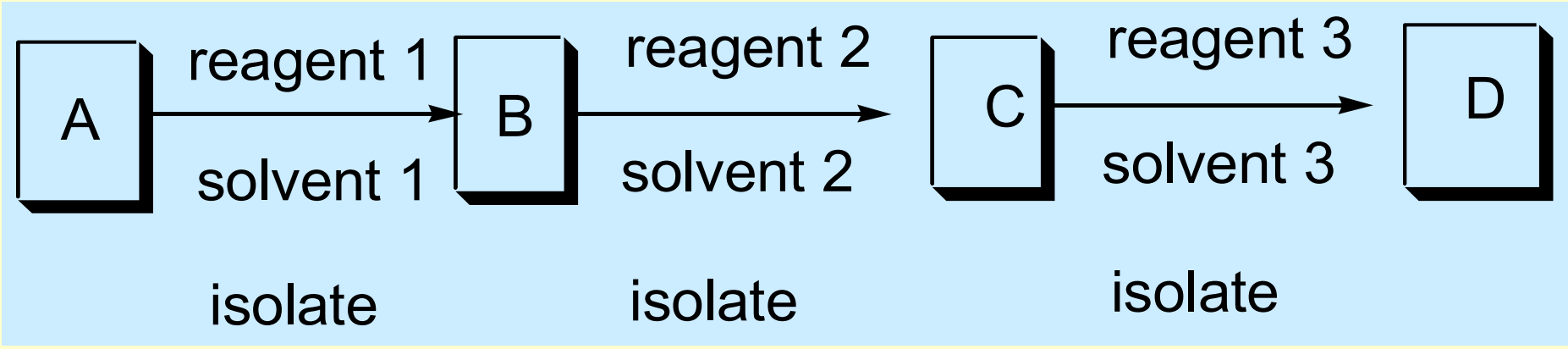
Cited by S. H. Bertz in "Complexity of Synthetic Reactions. The Use of Complexity Indices to Evaluate Reactions, Transforms and Disconnections", *New. J. Chem.* **2003**, *27*, 860.

* A quantitative understanding of synthetic efficiency is absent both from academic and pharmaceutical labs. Reliable indicators of synthetic efficiency are seldom developed and / or used.
* Both academic and even industrial (pharmaceutical) syntheses are still painfully inefficient.

DEVELOPING A ROUTE INTO A SCALABLE PROCESS

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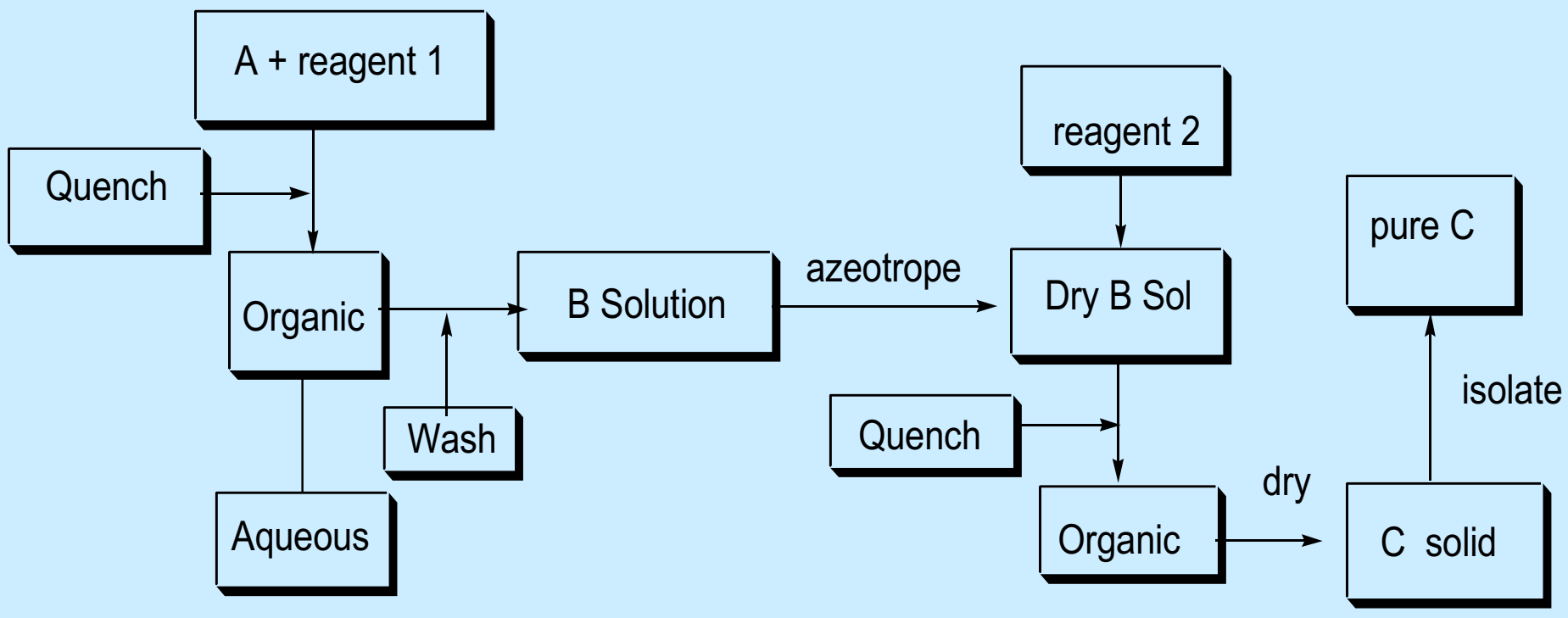
How an academic chemist thinks of a process:



Each step is thought of separately. Best conditions for each are identified, intermediates are isolated and characterized (NMR), then submitted to the next step.

HOW TO THINK LIKE A PROCESS CHEMIST

ABCD



Reactions, quenches, extractions, filtrations, are all "unit operations", which must be carefully planned and coordinat to maximize yield while utilizing minimum plant time (Volume – Time Requirements is related to cost of goods).

NEW METHODOLOGIES IN PROCESS CHEMISTRY

ABCD

New methodologies have clearly more impact on process than on discovery.

For example, it is generally more efficient to carry our catalytic reactions than stoichiometric ones. Asymmetric catalysis is, in principle, more efficient than separations or resolutions.

In catalysis, MUCH attention is paid to Turnover Numbers, i.e. catalyst robustness.

In 10 years at B.I. we have scaled up to pilot scale the following:
- Larock-type annulation
- Negishi cross-coupling
- Suzuki cross-coupling
- Palladium catalyzed enolate arylation
- Ring-closing metathesis
- Template-directed diastereoselective aldol reactions

BRIDGING THE GAP

ABCD

Academicians are doing well what they are supposed to do.

Process Chemistry is best done in industry, although a few academic institutions MAY CONSIDER having a curriculum in it (*i.e.* University of Zurich).

Students and postdocs are totally unaware of process chemistry. They do not understand it may be the most exciting career type available to them. The prejudice for discovery is usually based on ignorance both of discovery and development. Often this ignorance extends to the professor.

Steps that may be desirable:
- Synthetic students must be better trained in Physical Organic Chemistry.
- Introduce Process Chemistry short courses or workshops (from industrial chemists and engineers) in Ph.D. programs. Industrial PDs.
- Encourage students to read / discuss and publish in OPRD.
- More education of professors (contacts, conferences – Sciup conferences are a good mix but slanted towards industry).
- More involvement from process chemistry groups in educational activities.