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CHEMICAL SOCIETY REVIEWS (ISSN: 0306-0012) 43: 5387-5399 (2014)
DOI: 10.1039/C3CS60423C

Anthropogenic reaction parameters – the missing link between chemical intuition and the available chemical space*

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Abstract

How do skilled synthetic chemists develop such a good intuitive expertise? Why can we only access such a small amount of the available chemical space — both in terms of the reactions used and the chemical scaffolds we make? We argue here that these seemingly unrelated questions have a common root and are strongly interdependent. We performed a comprehensive analysis of organic reaction parameters dating back to 1771 and discovered that there are several anthropogenic factors that limit the reaction parameters and thus the scope of synthetic chemistry. Nevertheless, many of the anthropogenic limitations such as the narrow parameter space and the opportunity of the rapid and clear feedback on the progress of reactions appear to be crucial for the acquisition of valid and reliable chemical intuition. In parallel, however, all of these same factors represent limitations for the exploration of available chemistry space and we argue that these are thus at least partly responsible for limited access to new chemistries. We advocate, therefore, that the present anthropogenic boundaries can be expanded by a more conscious exploration of "off-road" chemistry that would also extend the intuitive knowledge of trained chemists.

Introduction

Considering the 69 million substances, 36 million scientific and patent records and more than 45 million reactions and synthetic preparations collected in Chemical Abstracts (CAS)[1], chemistry is by far the most productive scientific discipline. The known chemical space - represented by the number of substances in CAS - is growing faster than the world population.[2] The roughly 3 million chemists published more than 800,000 papers in 2007[1], which is considerably more than in other natural and social sciences.[3] The number of chemistry related patent applications reached 340,000 in 2009[4] which classifies chemistry as the second most inventive field after electrical engineering. Yet despite of these fascinating numbers, there are serious limitations of the collective knowledge domain of synthetic chemistry, the size of the synthetically explored chemical space[5] and the extent of scaffold diversity within its already explored region.

From a medicinal chemistry perspective, the estimated number of compounds to be considered when searching for new drugs (often called as the druglike space) is more than 10^{60} molecules.[6] This data indicates that the number of synthetically accessible compounds is

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much larger than mankind could ever synthesize. Computational tools, however, help enumerating of the accessible chemistry space and allow us to navigate towards regions with promising properties. Computer-aided structure elucidation techniques provide large virtual libraries such as GDB-13[7] and GDB-17[8] containing 977 million and 166.4 billion molecules of up to 13 and 17 atoms of C, N, O, S, and halogens, respectively. Enumeration methods include combinatorial linking of fragments, genetic algorithms based on cycles of enumeration or exhaustive enumeration from first principles. These enumerations show that >99.9% have never been synthesized and therefore they are not physically available.[9] Computational tools such as similarity searches,[10] property filtering[11] and virtual screening[12] however, are able to score and prioritize them for preparation and testing.
The other limitation of the already explored region of the chemical space is the scaffold diversity. Half of the compounds in the CAS Registry can be described by only 143 framework shapes and half of the 836708 known frameworks are only present in one single compound.[13] The limited diversity of structural frameworks is also reflected in the output of medicinal chemistry efforts. Half of the drugs in 1996 can be described by the 32 most frequently occurring frameworks[14] and the top 20 side chains represent 73 % of the total used in marketed drugs.[15] Virtually no improvement was observed during the last 10 years: the top 50 frameworks cover 48-52% of approved and experimental drugs.[16] These observations indicate that despite of the often-cited chemical intuition[17] of skilful chemists, scaffold diversity is limited in both organic and medicinal chemistry.

Chemical intuition is often evoked as a key element to account for important chemical discoveries and synthetic developments. It also allows experts to rapidly find a proper solution for a difficult chemical problem which otherwise would require a long time for a novice. We are always astonished how efficient an "educated guess" truly is, and how fast an expert organic chemist can suggest feasible alternatives to solve a synthetic chemical problem, e.g. selecting the appropriate reagents, solvents and reaction parameters. It is also very common that the initially selected parameters, reagents and catalysts are almost perfect, and it is often hard to find better conditions to improve the overall process. The value of chemical intuition is thus well recognised, but it has long been considered to be a mysterious mental process, whose role in the natural sciences is to suggest new research directions.

According to Herbert Simon — a Nobel Laureate in economics and pioneer of the decision-making theory and artificial intelligence[18] — however, intuition is better described as a phenomenon that is 'nothing more and nothing less than recognition'. According to Simon's cognitive approach,[19] intuition is a label for a process, a subconscious pattern recognition process based on experiences stored in long-term memory and retrieved when needed. Nevertheless, as Kahneman and Tversky[20,21] pointed out later, the accuracy and reliability of intuitive judgements[22] can vary significantly. In several cases the validity is questionable, often being bogus, because the intuitive thought is an *affect heuristic*, where decisions and judgements are subconsciously guided by feelings of liking and disliking, with marginal reasoning. To distinguish intuitions that are likely to be valid and useful, Klein and Kahneman propose[23] that not the expert's confidence, but the expert's background should be evaluated. If the experimentalist's environment is sufficiently regular and the person is able to learn its regularities, then there is a chance that the associative machinery will recognise patterns and generate quick and accurate predictions and decisions.

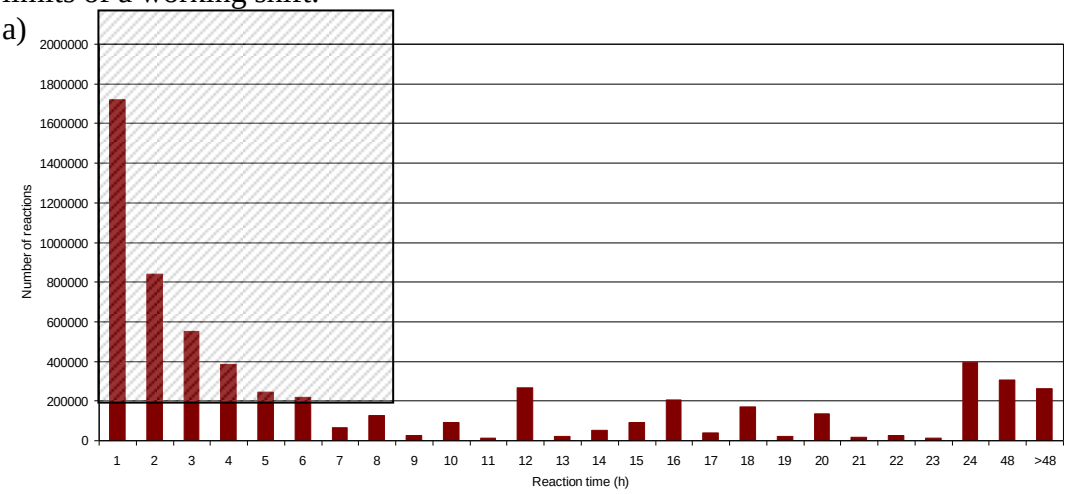
On this basis, it seems reasonable to investigate the background of organic chemists to address the question of whether a valid and reliable expert intuition could have been developed, or is an overvalued *affect heuristic*. However, instead of focusing on individuals,[24] it seems more valuable to analyse organic chemistry itself and use the chemical literature as a direct source and reflection of individuals' background.[25] Thus, we used an available

scientific database which is not only an excellent track record of discoveries, but also of methodologies and parameters.

The parameter space of chemical reactions

The chemistry knowledge accumulated between 1771 and 2011 was analyzed by collecting reaction parameters such as reaction time, temperature, pressure, solvent and yield from Reaxys (Figure 1).[26] Reaction time data for more than 6.3 million reactions suggest that about one third of the reactions take place within an hour, and half of the reactions are completed within less than 3 hours (Figure 1a). Less than 10% of the reactions need reaction times longer than 24 hours and only 3.7% run longer than 2 days. Considering the reactions performed within a day, we found that more than two third of the reactions are completed within 6 hours. Reaction times follow an almost exponential distribution with local maxima at 12 and 24 hours that most likely correspond to overnight reactions. Despite of these reactions the median reaction time for 4.5 million chemical reactions was found to be 3.3 hours. The average duration of reaction set-ups and work-ups extends the total time spent to almost 5 hours, which impacts the daily number of reactions performed within the anthropogenic[27] limits of a working shift.

a)



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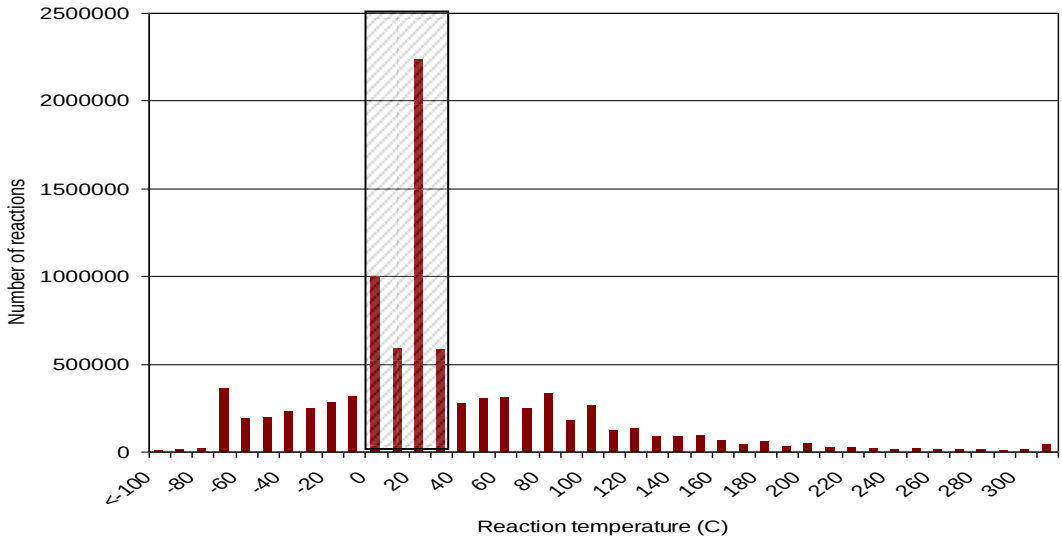

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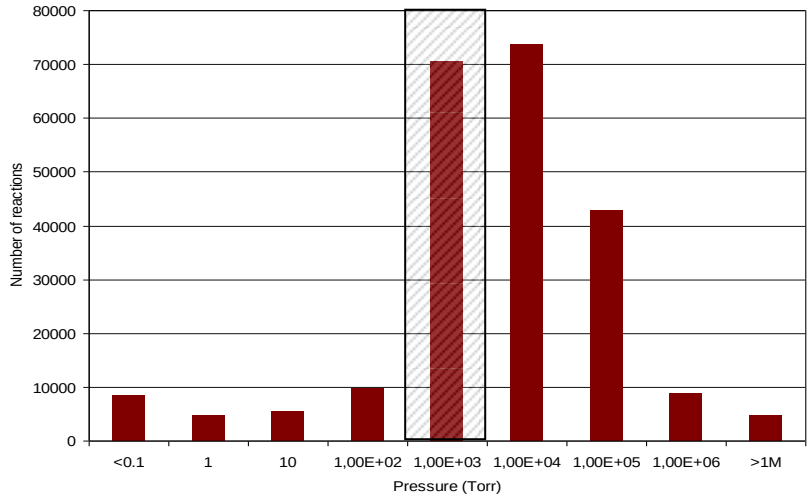


d)

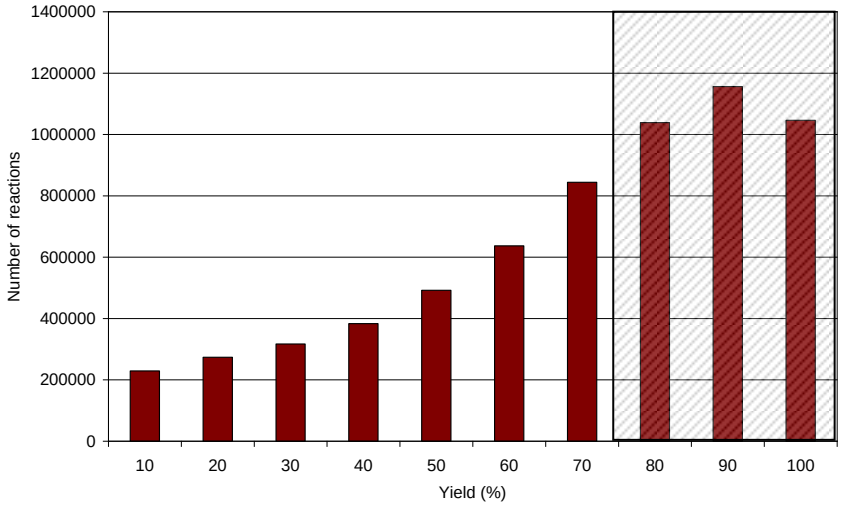


Figure 1. Relative distributions of reaction parameters in Reaxys. a) Reaction time; b) reaction temperature; c) reaction pressure; d) reaction yield. Anthropogenic ranges (duration of the working shift, ambient temperature, atmospheric pressure and high yield area, respectively) are shadowed. Cumulative distributions are available as supplementary material.

The number of available temperature data is somewhat higher (9.1 million) than that of the reaction times indicating that some of the reactions are performed at more than one temperature. Most of the reactions are realized between -80 °C and +200 °C (Figure 1b). In general, low temperatures are used less frequently than high temperatures, which can be readily rationalized by the reaction energetics and kinetics. Regarding the extremes less than 0.3% of the reactions use temperatures lower than -80 °C but 2% of the reactions need more than 200 °C indicating the higher incidence of technical difficulties at low temperatures.

Temperature distribution of chemical reactions is best described by a normal distribution, however, there are several local maxima that deviate significantly from that. The most frequent temperature is room temperature, which is the most convenient and therefore the most anthropogenic value within the range routinely used for chemical reactions. The second largest maximum is located around 0 °C which corresponds to ice bath cooling. There is another local maximum around -70 °C representing the utility of dry ice cooling in low temperature chemistry. Considering reactions between room temperature and 200 °C the median reaction temperature is 79.5 °C which is likely to be influenced by the most popular solvents. Clarifying this relationship we extracted the usage statistics of solvents referred more than thousand times from the total of 43 million citations. We found that out of these 84 solvents only 17 were used for 93% of reactions (Table 1). Interestingly, more than half of the reactions were performed in as few as five solvents. The usage corrected average boiling point of the 17 most popular solvents (78 °C) is pretty close to that of the median reaction temperature. This finding and other parameters of reaction energetics underline the impact of solvent selection on the reaction temperatures. Analyzing the polarity of the most popular solvents except for water we found that the usage corrected average polarity is 0.329. Consequently, most of the organic reactions are performed in apolar environment. Homogenous reactions therefore require apolar reactants that with the usual work-up protocols give strong preference to apolar products. One of the most important consequences of this finding is that it is challenging to prepare compounds with acceptable water solubility, a property of crucial importance in most drug discovery programs. Since human safety, health and environmental factors are often considered when selecting solvents for a chemical transformation, these anthropogenic decisions might have significant influence on the outcome of chemical reactions.

Table 1. Relative frequency and cumulative distribution of most referred solvents in Reaxys.

Solvent	***Bp. (°C)***	***Rel. polarity***[a]	***Relative %***	***Cumulative %***
Dichloromethane	39.8	0.309	15.17	15.17
Tetrahydofuran	66	0.207	14.84	30.00
Methanol	64.7	0.762	9.95	39.95
Water	100	1.000	7.77	47.72
Dimethyl formamide	153	0.386	7.56	55.28
Ethanol	78.3	0.654	7.11	62.39
Toluene	110.6	0.099	5.09	67.48
Diethylether	34.6	0.117	4.58	72.06
Acetonitrile	81.6	0.460	4.30	76.36
Benzene	80.1	0.111	3.61	79.97
Acetone	56.3	0.355	2.88	82.86
1,4-dioxane	101	0.164	2.36	85.22
Chloroform	61.2	0.259	1.83	87.04
Ethyl acetate	77.1	0.228	1.80	88.84
Dimethyl sulfoxide	189	0.444	1.47	90.31
Acetic acid	118	0.648	1.43	91.75
Pyridine	115.3	0.302	1.19	92.93
Other 67 solvents	-	-	7.07	100.00

[a]The values for relative polarity are normalized from measurements of solvent shifts of absorption spectra.[28]

As most of the reactions are performed at atmospheric pressure representing the most trivial choice it is not surprising that only 5% of the reaction entries have pressure data in Reaxys (Figure 1c). The strong preference for the atmospheric pressure is the consequence of its easiest realization that results another anthropogenic limitation of the present synthetic practice. Focusing on reactions performed under non-atmospheric pressure conditions, the distribution of pressures is asymmetric with a shift towards higher pressures. In fact, reactions realized above atmospheric pressure (82%) are at least four times more frequent than those performed below atmospheric pressure (18%). This corresponds to the fact that reactions with gases, i.e. most hydrogenation experiments, are performed under pressure and in general reactions below atmospheric pressure are technically much more challenging.
Finally we analyzed the reported yields on a dataset containing almost 6.5 million reactions (Figure 1d). Yields are complex measures reflecting not only the reactivity of the reaction components, the efficiency of the work up but also the optimization level of reaction parameters including those discussed previously. The level of optimization and the appropriate yield value that makes a reaction synthetically useful and worth to publish depends on many anthropogenic factors, including ethical and cultural aspects of scientific publication. Not surprisingly, the distribution of published yields is shifted towards high values with a maximum around 90%. Almost 75% of the published reactions have a yield exceeding 50% and half of the reactions produced yields higher than 80%. These data indicate that efficacy is one of the primary drivers and also an important criterion of synthetic research and publication strategies. Unfortunately, careful optimization of reaction parameters is avoided too often, which – in combination with efficacy criteria – might lead to interesting synthetic transformations with previously unknown products remaining unexplored and unpublished.

The trends observed in our analysis of 240 years of synthetic chemistry are not always surprising — because the analysis simply reflects the fact that reaction parameters in organic chemistry are highly anthropogenic and our environment functions as a mould. Chemists have been using the most obvious, often very convenient but somehow limited parameters for their experiments. A deeper scrutiny of this survey suggests, however, that while the overall trends may not be surprising, the limitations of key parameters are. The role of this serious parameter limitation appears both advantageous and critical; it provides sufficient regularities for experimentalists which are one of the prerequisites for developing valid and reliable expert intuition. The valid intuition's second condition is also fulfilled by the relatively short reaction time that automatically serves as a fast feedback mechanism and helps chemists to learn the regularities. Additionally, it seems plausible that these limited key parameters (which can be translated into a narrow range of activation energy) are critical to develop a certain "sense of energetics" in synthetic organic chemists. This knowledge has been automatically associated with structural formulae to evolve a hierarchical way of thinking; as exemplified in the functional group concept. Thus the graphical representation of atoms' and bonds' arrangement within molecules, which is a unique and discipline specific symbol system, is not purely qualitative in its nature and this "semi-quantitative" feature explains its enormous efficacy in synthesis design and development.

Can we reach the maximum synthetic output?

Despite the many major advances of the organic chemistry, and also the good and valid intuitive expertise of organic chemists, natural products show much larger scaffold diversity indicating that there are many more stable and feasible scaffolds outside the present domain of synthetic chemistry knowledge.[29] Although the limitation of the reaction parameters

undoubtedly leads structural limitation, we have to address additional questions: do we reach the maximum diversity that chemists could have achieved within the present limitations in the reaction parameters? If we consider the effect of these limitations as a kind of "structural parochialism", what is the impact of chemical intuition on that?
In pursuing these questions, we again turn to cognitive science and attempt to extend this knowledge towards organic chemistry. As a process of demystification Herbert Simon concluded that not only intuition, but also the scientific thinking is a kind of "nothing-special" phenomenon.[30,31] Simon argued that scientific discovery is a type of problem solving, so it's main characteristic is rather similar to everyday problem-solving methods. As defined, "the problem" is consisting of an initial state, a goal state and a set of permissible transformations between states, and constrains. The features of these main components can vary significantly and span a wide range of being well- to ill-defined. To illustrate this point, making a chemical discovery – in terms of cognitive science – is often a problem-solving process with an ill-defined goal state. Hence, for most of the scientific breakthroughs, there was no previous or direct intention to look for a new reaction or catalyst. Alternatively, upon pursuing a well-defined goal, useful but unexpected results may have been found — an outcome which is also welcomed. In contrast, developing a new drug or a new chiral catalyst is an example of a well-defined goal-state with an ill-defined initial state. The biggest task in these cases is to find appropriate constraints to complete the whole process within the allotted time.

In general, problem solving typically begins with constructing a representation for the problem, often described as a problem space in which the search for a solution should occur. For most synthetic chemistry problems, beside a thorough literature search, organic chemists also retrieve a representation stored in their memory and then this representation is fitted to the new situation using an analogical transfer. According to the Piaget's theory of schema this representation – often identified as expertise - can be defined as a set of sophisticated strategy.[32] The schemes can be extracted from the knowledge acquired by the exploration of the chemical space. Herbert Simon suggested[33] that intuition - the ability to know valid solutions to problems and decision making - is realized in a recognition process when scanning the actual problem to be solved against the accumulated scheme set. During this process one can create an intuitive solution by the unique combination of similar schemes (assimilation) or extending the present set a schemes (accommodation). Since the schema set of experts typically contains a large set of schemes they could use their base of experience to identify similar situations and intuitively choose feasible solutions.[34] Consequently, the anthropogenic factors that limit the explored chemical space help intuitive solutions in that they limit the scheme set to be screened.
This is in line with the finding of cognitive science that the current paradigms and legislations narrow the problem space, limiting the number of possible solutions. For example, using greener methodologies, applying cost-effective chemical production, avoiding the use of toxic and hazardous chemicals are recent challenges that create a narrower representation and limit the chemical space. Although many of these challenges can be solved by routine operations, organic chemists are more and more frequently unable to expand the problem space to fit the new problem, and are faced with the task of discovering an entirely different solution. Chemists then have to move into larger problem space, but an exhaustive search of all possible pathways is beyond human capacity. Hence, for an effective problem solving, a judiciously chosen set of constraints is applied to reduce the maze of possibilities to manageable proportions. The methods applied can be classified as either strong or weak methods depending on the specialist knowledge required to apply them.

Strong methods are typically employed by skilled experts because their accumulated knowledge allows the recognition of important clues in challenging problem situations. This intuition driven process facilitates the problem solving and the solution is generally found

with a minimum of effort. Like chess masters, who recognize a good move within a wink of an eye, experts in synthetic organic chemistry are able to heuristically[35] recognize the relevant components of a chemical problem, followed by a fast analysis of possible prospects and rapidly provide a solution including which synthetic strategy, reaction conditions, catalysts or reagents should be used. In both academic and industrial settings, high-level chemistry performance is directly related to the experts' deep knowledge acquired through prolonged studies and deliberate practice. Such strong methods, however, by their very nature, might result in a slow but thorough process to expand chemical space and structural diversity. On the other hand, strong methods often generate prejudices that prevent new directions being taken. New discoveries or the appearance of subfields within organic chemistry affect the quality and content of expertise, but their impact is delayed rather than immediate. Unfortunately, there is also precedent to suggest that some knowledge is not implemented and then forgotten.

Challenges that could not have been solved without fresh insight are typically treated by weak problem-solving methods. Such an approach usually requires less knowledge about the field and it has different variants, as among which the trial-and-error approach is the most common in chemistry. Recognizing, then analysing the result of unexpected chemical reactions has been the prerequisite of several important chemical discoveries such as Friedel-Crafts and Wittig reactions and hydroboration. While less efficient than so-called strong methods, the weak methods are of special interest and utility, because at the boundaries of knowledge the problems become less structured, and therefore intuitive recognition becomes less powerful. The clear advantage of this approach is that it secures a big expansion potential in organic synthesis and also in structural diversity. There have been several discoveries resulting from weak methods that opened new vistas in organic chemistry, such as Diels–Alder reaction, cross-couplings and olefin metathesis. The role of serendipity has not changed with the time, it has still an enormous value and impact on the evolution of pharmaceutical and organic chemistry.[36,37,38]

While strong and weak methods result, respectively, in slow and rapid expansion of chemical space, the balance of their practice is governed by the fact that chemists are satisficing — a word first coined by Simon that combines satisfy with suffice.[39] In their professional activity, the general task of organic chemists is to generate properties, such as an efficient chiral catalyst or drug. This often represents a formidable challenge and there is not enough time to generate all admissible alternatives and compare their respective merits. Therefore, the chemist does not have a choice between a satisfactory and optimal solution in their synthetic practice. That is to say, chemists often develop not an optimal but a satisfactory synthetic procedure, catalyst or drug molecule. We believe that an earmark of all these situations is the recognition of so-called privileged structures in drug[40] and catalysis[41] developments. The privileged structures are not necessarily the optimal structures, but the satisfactory structures that are synthetically easily available. This anchoring effect evidently slows down the search for new structures in both drug development and also in catalysis research. It is also not surprising that increasing time pressure stimulates risk-averse behaviour in both academia and industry which manifests itself in adhering more to privileged structures and current synthetic trends. A further roadblock to chemical discoveries can be demand from management for "chemical legal precedent", which often becomes decisive in continued funding.

The same satisficing attitude can also be seen when investigating reaction parameter space. Reaction temperatures, such as 25 °C (room temperature), 0 °C (ice bath), or the reflux temperature of a particular solvent (Figure 1b, Table 1) are typical examples of these preferences. These chosen temperature parameters may not always be optimal for a particular transformation. The same can be said for reaction pressure. Clearly, reactions under extreme

pressures (>10 kbar), the use of supercritical reaction environments, or methods like flash-vacuum pyrolysis are all known to synthetic chemists, and can sometimes offer unique synthetic possibilities not easily attained by other means.[42] The above-mentioned techniques are, however, generally perceived as being too impractical and thus are not used as often as they perhaps should be. In terms of reaction times, as we have already seen, organic chemists like to work with transformations that take several minutes to several hours, because using these time intervals allows us to monitor and control the reactions in a suitable, satisfying manner. If reactions are too fast (milliseconds or seconds) we have difficulties in following the progress of the reaction ("flash chemistry").[43] A related issue is reactor size. Synthetic chemists usually run reactions in centimetre size flasks, probably because the flask size is similar to the size of our hands. This reactor size is, however, very often not appropriate for controlling chemical transformations on a molecular level, particularly from the viewpoint of heat and mass transfer. Working in microstructured devices (microreactors) has many advantages and allows chemists to execute extremely fast chemical processes in a reliable manner as will be discussed below.[43,44] Limited availability of starting materials and reagents is another factor. Due to constraints on academic (training, promotion and grant timelines) and industrial (project timelines) research, synthetic chemists often limit their chemistry to readily available (= commercial) starting materials, building blocks, reagents, etc. Not surprisingly, therefore, we all use the same reagents and building blocks, and thus obtain similar scaffolds with limited diversity.

Interestingly, "structural parochialism" is not limited to chemistry. In their pivotal kinome studies Harlow and Knapp showed that most of the interest is focused to a relatively small set of protein kinases in both the scientific[45] and the patent literature,[46] respectively. As an extension of this work Edwards et al.[47] recently found that most protein research focuses on proteins known prior to the sequencing of the human genome. Investigating three classes of proteins with pharmaceutical relevance they found that research groups favoured the most well-known fraction of kinases, ion channels and nuclear receptors. Edwards et al. concluded that, in addition to anthropogenic factors — such as the desire of scientists to dig deeper and deeper into their particular research and the risk-averse nature of funding agencies and peer review systems — it is the availability of high quality tools that determines the research activity. Since studies on protein function and druggability typically require chemical biology tools, more specifically chemical probes, the limited diversity of available scaffolds has an obvious impact on the set of proteins investigated. Structural limitations therefore have knock-on effects in multiple disciplines within the life sciences.

How can we extend the available chemical space?

Having learned of the different strategies for tackling the maze of chemical discovery and practice, the most obvious question is: which method is the most efficient at expanding synthetic chemistry? General advice to 'think outside the box' to speed up discoveries is rather poorly defined and something of a rhetoric trope, but it does imply thinking unimpeded by constraints, and it is thus similar to weak methods. No constraints, however, mean also no hierarchy in problem space, so we should expect the success rate to be low. Nevertheless, this approach can lead to important advances, resulting in a "revolutionary" science. The opposite approach — perhaps an 'inside the box' approach — that relies on the hierarchy of chemical concepts and the particular chemist's experience does seem to be more productive in problem solving, but it affords slower development in synthetic chemistry. Thus, for the expansion of structural diversity, we conclude that strong methods are weak and the weak methods are strong. Nevertheless, a combination of the two can be a fruitful approach: after imposing

certain constraints to locate the experimental boundaries and hypothesis space it is then possible to begin application of a weak method.

Basically we see at least two overlapping options to expand the available chemistry space, and more importantly the present domain of synthetic chemistry knowledge. We can expand the anthropogenic boundaries in reaction parameters using enabling technologies and in parallel we should invest to discover new chemistries.

In the past few years organic chemists have increasingly looked at a number of so-called "enabling technologies" to escape some of the anthropogenic limitations described above (Figure 2).[48,49]

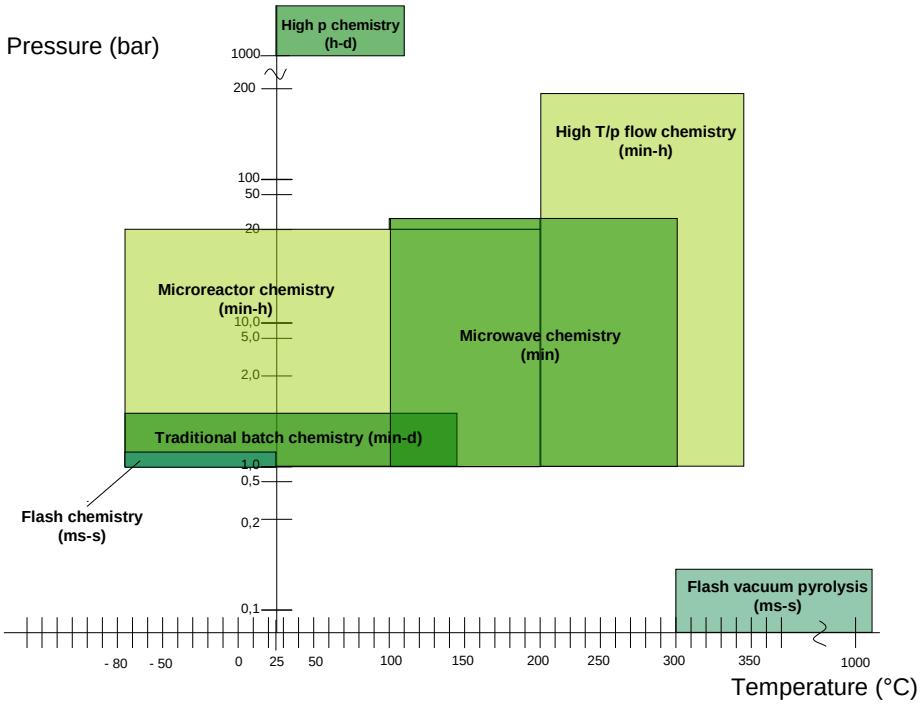


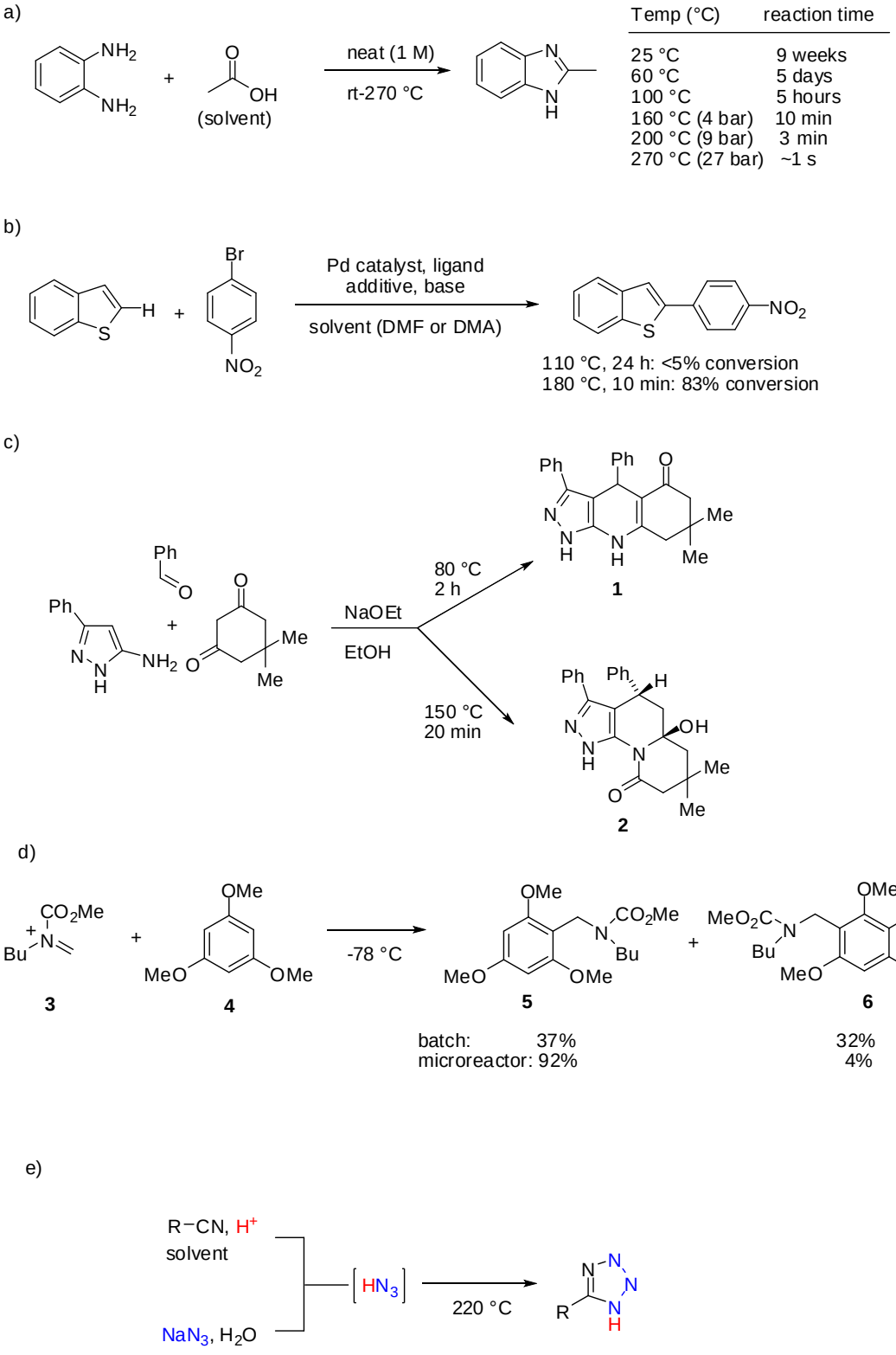
Figure 2 Enabling technologies expand the traditional temperature/pressure parameter space of chemical reactions. Typical reaction times are indicated in parentheses.

A plethora of promising new (and sometimes not so new) technologies are available to synthetic chemists today. In the context of extending available chemistry, the two most promising techniques are arguably microwave chemistry[50] and microreactor/flow technology.[43,44] In modern microwave instruments, synthetic transformations are typically carried out under sealed vessel (autoclave) conditions at temperatures up to 300 °C and a maximum operating pressure of 30 bar. This provides the chemist with the possibility to superheat reaction mixtures far above the boiling point of the solvent, and thus to move away from standard "reflux conditions" that have been the mainstay of synthetic chemistry for several centuries, resulting in the observed mean reaction temperatures discussed above (Figure 1b). Applying the Arrhenius equation, [$k = A \exp(-E_a/RT)$], it becomes apparent that the sometimes extreme temperatures observable in microwave chemistry allow reactions that require several hours at reflux can be completed in just a few minutes or even seconds using superheated solvents in an autoclave-type, microwave reactor. There are thousands of examples in the literature describe rate-enhancements in chemical transformations performed

using sealed vessel microwave technology demonstrating its role on the extension of the synthetically available chemical space[50] This is illustrated by a simple model transformation in Figure 3a. While the preparation of benzimidazole at room temperature requires 9 weeks to go to completion, at reflux conditions at 100 ^{o}C this transformation still involves 5 hours of heating in an oil bath. Switching to sealed vessel microwave technology the time can be shortened to 3 min at 200 ^{o}C or 1 second(!) at 270 ^{o}C.[51]
The ability to perform reactions within minutes rather than hours or days has had a major impact on the field of organic and medicinal chemistry in the past decade, and has revolutionized — particularly when coupled with suitable automation platforms — the way many pharmaceutical companies approach drug discovery today.[52] In the context of expanding chemical space, other features of microwave chemistry are, however, more important. Since microwave reactions are typically performed at a carefully optimized reaction temperature for the desired reaction pathway (no longer influenced by the boiling point of the solvent) these are in many instances cleaner transformations — leading to fewer byproducts. The sometimes significantly higher yields avoid time-consuming and costly isolation and purification issues, which is precisely why this technology is so popular in the drug discovery industry, where often dozens or even hundreds of derivatives of a particular scaffold need to be synthesized, and purification is a major cost factor.[52]

Most importantly, there are some transformations that simply do not work (or provide very low conversions) in a moderate temperature regime and can benefit significantly from the high temperatures attainable using microwave conditions. One of the many published examples is the palladium-catalyzed direct arylation of benzothiophene by an aryl bromide, (Figure 3b). At 110 °C reaction temperature this transformation provides <5% conversion after 24 h and is therefore of no practical synthetic value. At 180 °C under otherwise more or less identical reaction conditions the conversion is increased to 83% and the desired product can in fact be isolated in 75% yield, opening up a novel synthetic pathway to bi(hetero)aryl derivatives.[53]
In some instances, entirely novel chemical scaffolds have been obtained using microwave technology. In the multicomponent condensation shown in Figure 3c, a change in the reaction pathway was observed between the experiment carried out in refluxing ethanol (~80 °C) at atmospheric pressure, and the sealed-vessel microwave experiment at 150 °C. While the condensation reaction at reflux temperature provided the known tricyclic dihydropyridine derivative **1**, sealed vessel microwave heating of the same reaction mixture to 150 °C (14 bar) favored an alternative reaction pathway that led to the hitherto unknown pyrazolo[4,3-*c*]quinolizinone scaffold **2**.[54] While this surprising switch in selectivity is due to a simple thermal effect,[55] this example illustrates nicely that the parameter space accessible by microwave processing can sometimes lead to unexpected products, favoring reaction pathways not seen under conventional processing at lower (often reflux) temperatures.

Figure 3 | The impact of enabling technologies on the anthropogenic boundaries. a) Enhanced reaction speed using sealed vessel microwave conditions; b) Improved yields using microwave conditions; c) Altered reaction pathways applying microwave conditions; d) Improved selectivity using "flash chemistry"; e) Hazardous reaction conditions possible using flow chemistry.



Another technique that is gaining popularity in the synthetic chemistry community is microreactor technology.[43,44] Microreaction technology is generally defined as the continuous flow processing of reactions within structured channels of less than 300 μm diameter. Because of the high surface-to-volume ratio in microchannels of this type, heat transfer is very efficient and reaction temperatures in microreactors can be changed efficiently by application or removal of heat. Importantly, due to the microstructured environment, mixing is very efficient and therefore even very rapid chemical reactions – where the reaction time is faster than the mixing time – can be reliably performed using microreaction technology. A key factor is the accurate control of the residence time in the continuous flow environment that can influence the observed selectivity.[43,44] Numerous applications of microreaction technology (e.g. Figure 3d) where rapid heat and mass transfer are essential to the success of extremely rapid chemical transformations (sometimes referred to as "flash chemistry") have been reported in the literature.[43]
Another area where microreaction technology (or flow chemistry in general) has been applied to extend the normal reaction parameter space of organic chemists is the concept of "Novel Process Windows". Here, the general notion is to operate at conditions which considerably speed up conversion rates, while maintaining selectivity. This is achieved by, for example, step-change increases in temperature and pressure or by a simplification of process protocols.[56,57] Although this is in some ways similar in concept to microwave heating, a clear advantage of performing high-temperature/high-pressure (high-T/p) chemistry under continuous flow conditions is that significantly higher pressures can be attained in a flow environment, and the ability to scale the desired chemistry to production volumes.[44] Another key advantage in the use of microreactors is that synthetic intermediates can be generated and consumed in situ — eliminating the need to store toxic reactive of explosive intermediates and thus making the protocol safer. Figure 3e illustrates the safe use of hydrazoic acid, an extremely explosive and toxic material, generated in situ in a microreactor for the synthesis of tetrazoles in a continuous flow regime is highlighted.[58]. The chemical intuition of most traditional chemists would strictly avoid reactions of this type, particularly at the high temperatures applied. In this context microreactor technologies provide viable alternatives expanding the available chemical space. Until now, microreactor technology has mainly been applied by the chemical manufacturing and engineering communities to improve the efficiency of (often known) chemical processes. This is now changing and it can be expected that this enabling technology will be very useful to generate new chemical scaffolds and to thus to expand chemical space. Pharmaceutical R&D is clearly one of the first sectors introducing continuous flow syntheses in discovery and process chemistry settings.[59]
In the context of the cognitive approach enabling technologies are strong methods that mainly allow thinking inside the box. These techniques extend the previously available range of reaction parameters including reaction temperature, pressure and reaction time. The increasing use of microwave technology,[50,52] microreactor chemistry,[43,44] flow procedures and flash chemistry,[43] however can not replace intuitive discoveries that can result in new reactions and completely new chemistries. The farseeing exploration of new opportunities within the present knowledge space could only be realized by weak methods that have verified their utility several times in the history of organic chemistry.

We now attempt to locate what we regard as some of the present "boundaries" —fields of research within organic chemistry that we think have a potential to expand the knowledge space of synthetic organic chemistry in the near future. Inventions related to new types of reactivity are the typical examples of such out of the box research. Our selection of examples involves homogenous gold catalysis, C-H activation and frustrated Lewis pair chemistry and

necessarily far from complete but demonstrates the power of weak methods in the expansion of the available chemical space.
Gold and its complexes have been long considered to be rather poor catalysts with limited utility, however, recent advances in homogeneous gold catalysis have sharply contradicted this presumption. The strong and selective π acidity of the gold complexes, coupled with their potential to stabilize cationic intermediates, enabled unique catalytic reactivity that would be difficult to achieve by other metal or activation mode.[60]. It has been demonstrated that gold complexes are able promote a cycloisomerisation, cycloaddition and sigmatropic rearrangement, oxidative couplings and enantioselective catalysis, thus gold catalysis has become the "the gold standard" in versatility and performance for carbo- and heterocycles and natural products synthesis.[61,62]

The challenge to develop a selective catalytic transformation of an arbitrary C-H bond into a more reactive functionality under mild condition is the Holy Grail of catalysis.[63,64] The enormity of the task here is reflected in our standard notation system — simple C–H bonds are usually considered so unreactive that the hydrogens are usually omitted in Lewis structures. Although C-H activation has historically rest upon radical chemistry, there is a fundamental shift in research focus nowadays due to selective C-H activation capacity of transition metals in arenes and alkanes. Several coordination-directed C-H activation methodologies have been reported which could discern different type of C-H bonds indicating the future potential of this chemistry. The further expansion of the selective C-H activation would not only be a new possibility in total synthesis in general, but also could increase the speed of synthetic capacity exponentially, in a non-conventional manner.

The field of frustrated Lewis pair chemistry (FLP),[65,66] an immensely important area of chemistry, originates from the fact that sterically congested Lewis acid-base pairs are not able to form a classical donor-acceptor complex, thus the unquenched nature of these systems can be exploited for several unique and unprecedented transformations. In this manner, enormous strain can be released upon activation which unique activation mode has so far been the exclusive feature of enzymatic catalysis. The most outstanding FLP reactivity discovered is the metal-free activation of hydrogen at ambient conditions — boron–phosphorus or boron–nitrogen FLPs have been used to achieve a metal-free catalytic hydrogenation. The field of frustrated Lewis pairs perhaps the least developed of the three areas we have chosen to highlight and a large body of fundamental chemistry remains to be investigated but the achievements so far suggest to us that it may lead to a significant shift in catalyst design and development. In fact, FLPs often behave like transition metals and are able to react with a variety of functionalities. Further steric tuning could open the way for unusual reaction selectivities. For example, hydrogenation of C=C double bonds can be achieved selectively in the presence of more reactive functionality.[67,68] Since FLP is a general concept for dual activation utilizing extremely strong acid and base together, we expect that a lot of new reactivity will emerge which is expected to foster new chemistry and the synthesis of new scaffolds.

Another option of expanding the present boundaries is to create new synthetic platforms to join molecular pieces efficiently and rapidly to each other. These synthetic strategies would maximize the capacity of already known chemistries and help the effective sampling of the chemistry space provided by newly discovered reactivities. Within the vast available tools of molecular connectivity, we think that the following approaches have and will have a foreseeable potential: the domino or cascade reactions, click chemistry and combinatorial approaches.
Domino or cascade reactions enable synthetic chemists to build complex structures in one-pot reactions in a highly orchestrated multistep sequence.[69] Among many possibilities, the

development of multicomponent organocatalytic reactions has a particular importance since this approach closely resembles endogenous biosynthetic pathways producing the high structural variety of natural products.[70] From simple building blocks, several assembly lines can be conceived which provide densely functionalized chiral molecules with 3-6 contiguous chiral centres.[71] Organocascade and organoiterative approaches obviously allow the expansion of structural diversity in organic chemistry and are expected to have an impact on total synthesis strategies.[72] Additionally, we believe that this powerful tool should be considered as a strategic methodology for future medicinal chemistry developments. Not only patentable structures, but also a multitude of natural-product-like structures with advantageous physico-chemical properties can be assembled in a fast and robust manner. This would represent a notable departure from today's pharmaceutical practice, from the (hetero)aryl flatland chemistry.[73]

The click reactions are a set of powerful, reliable, but highly selective reactions that can be utilized for the rapid construction of new compounds and combinatorial libraries. The concept was introduced by Sharpless, Kolb and Finn[74] and have gained widespread applications ranging from drug discovery, material science, nanotechnology, and bioconjugation.[75,76,77] Further expansion of the click reaction diversity and the field of applicability of this straightforward synthetic strategy is expected in future which can fundamentally contribute to creation of molecules with novel and desired function.

Combinatorial chemistry aims to prepare a large number of compounds in a single process. This approach is a tour de force undertaking to generate a desired molecular property. The original methodology has been advanced to build in some evolutionary element into the synthesis using a dynamic approach.[78] Additionally, a fundamental but still unexplored alternative has been developed: the DNA-programmed combinatorial chemistry.[79,80,81] In this case the DNA functions as a gene and orchestrates the assembly of small molecular components. Combined with the techniques of molecular biology, a molecule with a desired property can be evolved. Compared to the classical chemical synthesis, this technique would allow the mapping of a markedly larger chemical space in a rapid manner, thus it can have an enormous potential in future chemistry.

Although the few examples discussed here cannot demonstrate the scope and importance of new chemistries in expanding the anthropogenic limits, however, they exemplify how weak problem-solving could contribute to the extension of the synthetic chemistry knowledge space and the intuitive chemistry domain.

Conclusion

Based on the analysis of a large set of chemical reactions, we found that anthropogenic factors limit the reaction parameters and thus the scope of synthetic chemistry. The limitation of reaction parameters appears to be of critical importance but interestingly it is also advantageous. On the one hand, these factors contribute significantly to the markedly narrow parameter space applied in organic syntheses and consequently - with other components - they are responsible for the limited chemistry space explored to date. On the other hand, however, they provide sufficient regularities for experimentalists that facilitate developing valid and reliable expert intuition. Anthropogenic factors therefore represent a link between chemical intuition and the available chemistry space.

Applying the results of cognitive science we argue that the methods typically applied in problem solving and decision making have an additional impact on the present limits of organic chemistry knowledge and chemical space. Classifying applied methods as either strong or weak methods it is possible to observe that strong methods are typically used by skilled experts and could result in a slow but thorough process to expand chemical space and

structural diversity. In contrast, there are fundamental challenges requiring weak approaches of problem solving. Although these methods are often less efficient they present considerable advantages at the boundaries, where expert intuition becomes less powerful. Our understanding is therefore that the strong methods are weak and the weak methods are strong in the expansion of chemical space and structural diversity. It seems that organic chemistry would benefit most from their special combination as strong methods help locating the present boundaries, while weak methods would suggest escape routes towards new findings.

We strongly believe that being aware of anthropogenic limits and its consequences would facilitate the conscious extension of the organic chemistry knowledge space (Figure 4).

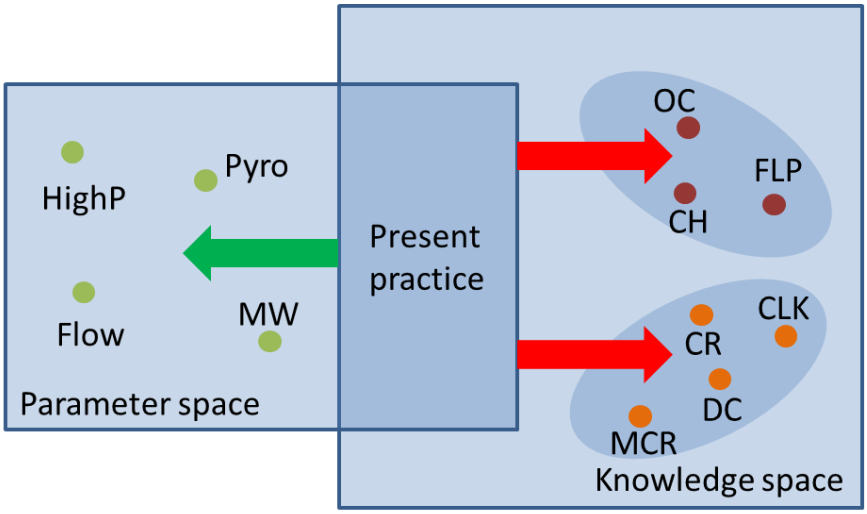


Figure 4 The impact of weak and strong methods on the parameter and knowledge space of synthetic organic chemistry. Weak methods, represented by red arrows, extend the knowledge space at least by two means. Discovering new reactivities (dark red dots), exemplified by organocatalysis (OC), frustrated Lewis pairs (FLP) and C-H activation (CH) opens new roads to the previously unexplored chemistry space. New synthetic platforms (orange dots) such as cascade reactons (CR), dynamic chemistry (DC), click chemistry (CLK), and multicomponent reactions (MCR) improve the sampling of the knowledge space. Enabling technologies (green dots) such as high pressure chemistry (HighP), microwave technology (MW), flash pyrolysis (Pyro) and microreactor flow chemistry (Flow) expand the parameter space of chemical reactions.

Technological improvements such as microwave, “flash” and flow chemistry expand the parameter space toward the “off-road” chemistry space. These technologies might contribute significantly to reach previously unexplored chemistry space by making new reactions available, extending the scope of known reactions and improving their overall performance. Moving deliberately toward extremities in parameter space, intuitive approaches such as reaction and reagent design and catalytic initiatives enhance the chance to find Terra Incognita in chemistry with potential impact on the expansion of the chemical space and also the knowledge domain of organic chemistry.

Acknowledgement
The authors thank the many scientists who have contributed to the ideas presented in this Perspective, in particular György Domány, János Éles, György Túrós and Zsuzsa Hadady (Gedeon Richter), István Kolossváry (D.E. Shaw Research), Zoltán Kovári (Kovári Patent

Attorneys' LLC), Ferenc Fülöp (University of Szeged), Georg Fráter (Xi-Mo AG), István Czigler, Attila Demeter, Imre Pápai, Imre Bakó, Szilárd Varga (Research Centre for Natural Sciences, Hungarian Academy of Sciences). C.O.K acknowledges the Christian Doppler Research Foundation (CDG) for financial support. T.S. thanks for the support of Lendület programme of the Hungarian Academy of Sciences.

Reference

1 Chemical Abstract Service, www.cas.org, Columbus, OH 43210-0012, USA, 2008
2 Schummer, J. Coping with the Growth of Chemical Knowledge. Challenges for Chemistry Documentation, Education, and Working Chemists. *Ed. Quím.* 1999, **10**, 92-101.
3 Larsen, P O., von Ins, M. The rate of growth in scientific publication and the decline in coverage provided by Science Citation Index. *Scientometrics* 2010, **84**, 575–603.
4 World Intellectual Patent Organization, WIPO Statistics Database, 2011, http://www.wipo.int/export/sites/www/freepublications/en/intproperty/941/wipo_pub_941_2011.pdf)
5 According to the definition, chemical space is the space spanned by all possible (i.e. energetically stable) molecules and chemical compounds in all possible topology isomers.
6 Bohacek, R. S., McMartin, C., Guida, W. C. The Art and Practice of Structure-Based Drug Design: A Molecular Modeling Perspective. *Med. Res. Rev.* 1996, **16**, 3-50.
7 Blum, L. C., Reymond, J. L. 970 Million Druglike Small Molecules for Virtual Screening in the Chemical Universe Database GDB-13. *J. Am. Chem. Soc.* 2009, **131**, 8732-8733.
8 Ruddigkeit, L., van Deursen, R., Blum, L. C., Reymond, J. L. Enumeration of 166 Billion Organic Small Molecules in the Chemical Universe Database GDB-17. *J. Chem. Inf. Model.* 2012, **52**, 2864-2875.
9 Reymond, J. L., Awale, M. Exploring Chemical Space for Drug Discovery Using the Chemical Universe Database. *ACS Chem. Neurosci.* 2012, **3**, 649-657.
10 Eckert, H., Bajorath, J. Molecular Similarity Analysis in Virtual Screening: Foundations, Limitations and Novel Approaches. *Drug Discov. Today.* 2007, **12**, 225-233.
11 Athanasiadis, E., Cournia, Z., Spyrou, G. ChemBioServer: A Web-Based Pipeline for Filtering, Clustering and Visualization of Chemical Compounds Used in Drug Discovery *Bioinformatics* 2012, 28, 3002-3003.
12 Sotriffer, C. (Editor), Mannhold, R. (Series Editor), Kubinyi, H. (Series Editor), Folkers G. (Series Editor) Virtual Screening: Volume 48 - Principles, Challenges, and Practical Guidelines (Methods and Principles in Medicinal Chemistry), Wiley-VCH, New York, USA, 2011.
13 Lipkus, A. H., Yuan, Q., Lucas, K. A., Funk, S. A., Bartelt III, W. F., Schenck, R. J., Trippe, A. J. Structural Diversity of Organic Chemistry. A Scaffold Analysis of the CAS Registry. *J. Org. Chem.* 2008, **73**, 4443-4451.
14 Bemis, G. W., Murcko, M. A. The Properties of Known Drugs. 1. Molecular Frameworks. *J. Med. Chem.* 1996, **39**, 2887-2893.
15 Bemis, G. W., Murcko, M. A. Properties of known drugs. 2. Side chains. *J. Med. Chem.* 1999, **42**, 5095-5099.
16 Wang, J., Hou, T. Drug and Drug Candidate Building Block Analysis. *J. Chem. Inf. Model.* 2010, **50**, 55–67.
17 Intuition is the ability to acquire knowledge without inference or the use of reason. In more-recent psychology, intuition can encompass the ability to know valid solutions to problems and decision making.
18 Feigenbaum, E. A. Herbert A. Simon, 1916-2001 *Science* 2001, **291**, 2107.
19 Simon, H. A. What Is an "Explanation" of Behavior? *Psychol. Sci.* 1992, **3**, 150-161 .

20 Tversky, A., Kahneman, D. Judgment under Uncertainty: Heuristics and Biases- *Science* 1974, **185**, 1124-1131.
21 Kahneman, D. Thinking, Fast and Slow, Farrar, Straus and Giroux, New York, 2011.
22 Gibb, B. C. Chemical intuition or chemical institution? Nature Chem. 2012, **4**, 237–238 (2012)
23 Kahneman D., Klein G. Conditions for intuitive expertise: A failure to disagree. *Am. Psychol.* 2009, **64**, 515-526.
24 Kutchukian, P. S., Vasilyeva, N. Y., Xu, J., Lindvall, M. K., Dillon, M. P., Glick, M., Coley, J. D., Brooijmans, N. Inside the Mind of a Medicinal Chemist: The Role of Human Bias in Compound Prioritization during Drug Discovery. *PLoS ONE* 2012, **7**, e48476.
25 The importance of the structure of the environment to which cognition is adapted, see: Anderson , J. R. The Adaptive Character of Thought. Hillsdale, New Jersey, Erlbaum Associates, 1990.
26 Reaxys database, 2012 Elsevier Properties SA (accessed on 3rd January, 2012)
27 The term anthropogenic designates an effect, process or object resulting from human activity.
28 Reichardt, C. Solvents and Solvent Effects in Organic Chemistry, Wiley-VCH: Weinheim, 2003.
29 Grabowski, K., Schneider, G. Properties and Architecture of Drugs and Natural Products Revisited. *Curr. Chem. Biol*. 2007, **1**, 115-127.
30 Simon, H. A., The Sciences of the Artificial, The MIT Press, 1996.
31 Klahr, D. Exploring Science, The MIT Press, 2000.
32 Inhelder, B., Chipman, H. H., Zwingmann, C. (Eds.) Piaget and His School, Berlin, Germany, Springer, 1976.
33 Simon, H. A. What Is an "Explanation" of Behavior? *Psychological Science* 1992, **3**, 150-161.
34 Klein, G. A. Sources of Power: How People Make Decisions. Cambridge, USA, MIT Press, 1999.
35 Graulich, N., Hopf, H., Schreiner, P. R. Heuristic thinking makes a chemist smart. *Chem. Soc. Rev.* 2010, **39**, 1503-1512.
36 Munos, B. A Forensic Analysis of Drug Targets From 2000 Through 2012. *Clinical Pharmacology & Therapeutics* 2013, **94**, 407-411.
37 Morley, A. D., Pugliese, A., Birchall, K., Bower, J., Brennan, P., Brown, N., Chapman, T., Drysdale, M., Gilbert, I., Hoelder, S., Jordan, A., Ley, S. V., Merritt, A., Miller, D., Swarbrick, M. E., Wyatt, P. G. Fragment-based Hit Identification: Thinking in 3D, *Drug Discov. Today*, 2013**, 18**, 1221–1227.
38 McNally, A., Prier, C. K., MacMillan, D. W. C. Dicovery of an a-Amino C-H Arylation Reaction Using the Strategy of Accelerated Serendipity *Science* **2011**, *334*, 1115.
39 Manktelow, K. Reasoning and Thinking, Hove, Psychology Press, p. 221 (2000).
40 DeSimone, R. W., Currie, K. S., Mitchell, S. A., Darrow, J. W., Pippin, D. A. Privileged structures: applications in drug discovery. *Comb. Chem. High. Throughput Screen.* 2004, **7**, 473-94.
41 Yoon, T. P., Jacobsen, E. N. Privileged Chiral Catalysts. *Science* 2003, **299**, 1691–1693.
42 Chemistry under Extreme or Non-Classical Conditions, van Eldik, R.; Hubbard, C. D., Eds. J. Wiley & Sons, New York, 1997.
43 Yoshida, J.-i. Flash Chemistry - Fast Organic Synthesis in Microsystems, Wiley-VCH: Weinheim, 2008.
44 Wiles, C.; Watts, P. Micro Reaction Technology in Organic Synthesis; CRC Press, Boca Raton, 2011**.**
45 Grueneberg, D. A., Degot, S., Pearlberg, J., Li, W., Davies, J. E., Baldwin, A. Endege, W., Doench, J., Sawyer, J., Hu, Y., Boyce, F., Xian, J., Munger, K., Harlow, E. Kinase

requirements in human cells: I. Comparing kinase requirements across various cell types." *Proc Natl Acad Sci U S A* 2008, **105**, 16472-7.
46 Fedorov, O., Muller, S., Knapp, S. The (un)targeted cancer kinome. *Nature Chem. Biol.*2010, **6**, 166-169.
47 Edwards, A. M., Isserlin, R., Bader, G. D., Frye, S. V., Willson, T. M., Yu, F. H. Too many roads not taken. *Nature* 2011, **470**, 163-165.
48 Ley, S.V., Baxendale, I.R. The changing face of organic synthesis. *Chimia* 2008, **62**, 162-168.
49 O'Brien, M., Denton, R., Ley, S.V. Lesser-Known Enabling Technologies for Organic Synthesis. *Synthesis* 2011, **42**, 1157-1192.
50 Kappe, C. O.; Stadler, A.; Dallinger, D. Microwaves in Organic and Medicinal Chemistry, *2nd Ed.*, Wiley-VCH: Weinheim, 2012.
51 Damm, M., Glasnov, T. N., Kappe, C. O. Translating High-Temperature Microwave Chemistry to Scalable Continuous Flow Process. *Org. Process. Res. Develop.* 2010, **14**, 215-224.
52 C. O. Kappe, D. Dallinger, The Impact of Microwave Synthesis on Drug Discovery, *Nature Rev. Drug Discov.* 2006, **5**, 51-63.
53 M. Baghbanzadeh, C. Pilger, C. O. Kappe, Palladium-Catalyzed Direct Arylation of Heteroaromatic Compounds: Improved Conditions Utilizing Controlled Microwave Heating. *J. Org. Chem.* **76**, 8138-8142 (2011).
54 V. Chebanov, V. Saraev, S. Desenko, V. Chernenko, I. Knyazeva, U. Groth, T. Glasnov, C. O. Kappe, Tuning of Chemo- and Regioselectivities in Multicomponent Condensations of 5-Aminopyrazoles, Dimedone and Aldehydes. *J. Org. Chem.* **73**, 5110-5118 (2008).
55 D. Obermayer, B. Gutmann, C. O. Kappe, Microwave Chemistry in Silicon Carbide Reaction Vials: Separating Thermal from Nonthermal Effects. *Angew. Chem. Int. Ed.* **48**, 8321-8342 (2009).
56 Hessel, V. Novel Process Windows – Gate to Maximizing Process Intensification via Flow Chemistry. *Chem. Eng. Technol.* 2009, **32**, 1655-1681.
57 Hessel, V., Cortese, B., de Croon, M. H. J. M. Novel process windows – Concept, proposition and evaluation methodology, and intensified superheated processing. *Chem. Engin. Sci.* 2011, **66**, 1426-1448.
58 Gutmann, B., Roduit, J.-P., Roberge, D., Kappe, C. O. Synthesis of 5-Substituted 1*H*-Tetrazoles from Nitriles and Hydrazoic Acid Using a Safe and Scalable High-Temperature Microreactor Approach. *Angew. Chem. Int. Ed.* 2010, **49**, 7101-7105.
59 Malet-Sanz, L., Susanne, F., Continuous flow synthesis. A pharma perspective. *J. Med. Chem.* 2012, **55**, 4062–4098.
60 Hashmi, A. S. K. Homogeneous Gold Catalysis Beyond Assumptions and Proposals—Characterized Intermediates. *Angew. Chem. Int. Ed.* 2010, **49**, 5232–5241.
61 Arcadi, A. Alternative Synthetic Methods Through New Developments in Catalysis by Gold. *Chem. Rev.* 2008, **108**, 3266-3325.
62 Li, Z. G., Brouwer, C., He, C. Gold-Catalyzed Organic Transformations. *Chem. Rev.* 2008, **108**, 3239-3265.
63 Arndtsen, B. A., Bergman, R. G., Mobley, T. A., Peterson, T. H. Selective Intermolecular C-H Bond Activation by Synthetic Metal Complexes in Homogeneous Solution *Acc. Chem. Res.* 1995, **28**, 154-162.
64 themed issue reviewing the latest applications in C-H functionalization: *Chem. Soc. Rev.* 2011, **40**, 1855-2038.
65 Welch, G. C., San Juan, R. R., Masuda, J. D., Stephan, D. W. Reversible, metal-free hydrogen activation. *Science* 2006, **314**, 1124–1126.
66 Stephan, D. W., Erker, G. Frustrated Lewis pairs: metal-free hydrogen activation and more. *Angew. Chem. Int. Ed.* 2010, **49**, 46–76.

67 Erős, G., Mehdi, H., Pápai, I., Rokob, T. A., Király, P., Tárkányi, G., Soós, T. Expanding the scope of metal-free catalytic hydrogenation through frustrated Lewis pair design. *Angew. Chem. Int. Ed.* 2010, **49**, 6559–6563.
68 Soós, T. Design of frustrated Lewis pair catalysts for metal-free and selective hydrogenation. *Pure and Appl. Chem.* 2011, **83**, 667–675.
69 Tietze, L. F., Brasche, G., Gericke, K. Domino Reactions in Organic Synthesis, 2006, Wiley, New York, USA.
70 Enders, D., Grondal, C., Hüttl, M. R. M. Asymmetric organocatalytic domino reactions. *Angew. Chem. Int. Ed.* 2007, **46**, 1570-81.
71 Enders, D. Hüttl, M. R. M., Grondal, C. Raabe, G. Control of four stereocentres in a triple cascade organocatalytic reaction. *Nature* 2006, **441**, 861-3.
72 Grondal, C., Jeanty, M., Enders, D. Organocatalytic cascade reactions as a new tool in total synthesis. *Nat. Chem.* 2010, **2**, 167–178.
73 Lovering, F., Bikker, J., Humblet C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* 2009, **52**, 6752-6756.
74 Kolb, H. C., Finn, M. G., Sharpless, K. B. Click Chemistry: Diverse Chemical Function from a Few Good Reactions. *Angew. Chem. Int. Ed.* 2001, **40**, 2004-2021.
75 themed issue reviewing the latest applications of click chemistry: *Chem. Soc. Rev.* 2010, **39**, 1231-1405.
76 Moses, J. E., Moorhouse, A. D. The growing applications of click chemistry. *Chem. Soc. Rev.* 2007, **36**, 1249-1262.
77 Lahann J. (Ed.) Click chemistry for biotechnology and material science. **2009**, Wiley, New York, USA.
78 Greaney, M. F. Bhat, V. T. Protein-directed dynamic combinatorial chemistry. In Dynamic combinatorial chemistry: in drug discovery, bioinorganic chemistry, and materials sciences. Miller, B. L., Ed.; John Wiley & Sons: New Jersey, **2010**; Chapter 2, 43.
79 Gartner, Z. J., Liu, D. R. The generality of DNA-templated synthesis as a basis for evolving non-natural small molecules. *J. Am. Chem. Soc.* 2001, **123**, 6961-6963.
80 Gartner, Z. J., Tse, B. N., Grubina, R., Doyon, J. B., Snyder, T. M., Liu, D. R. DNA-templated organic synthesis and selection of a library of macrocycles. *Science* 2004, **305**, 1601-1605.
81 Weisinger, R.M., Wrenn, S. J., Harbury, P. B., Highly parallel translation of DNA sequences into small molecules. *PloS ONE* 2012, **7**, e28056.

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