Green chemistry metrics for organic synthetic chemistry

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CONTENTS

ABBREVIATIONS

ACS	American Chemical Society
AE	Atom economy
AP	Acidification potential
API	Active Pharmaceutical Ingredient
C-C	Carbon-Carbon (bond)
CE	Carbon Efficiency
cEF	Complete E-factor
DMA	Dimethyl Acetamide
EATOS	Environmental Assessment Tool for Organic Synthesis
EF	E-factor
E-factor	Environmental Factor
EPA	Environmental protection agency (in the US)
EQ	Environmental Quotient
EU	European Union
EuP	Eutrophication Potential
FLASC	Fast Life Cycle Assessment of Synthetic Chemistry
GAL	Green Aspiration Level
GCI	Green Chemistry Institute
LCA	Life Cycle Assessment
LCI	Life Cycle Inventory
LCIA	Life Cycle Inventory Assessment
MI	Mass Intensity
MSDS	Material Safety Data Sheet
Mw	Molecular weight

NBS	*N*-Bromosuccinimide
PMI	Process mass intensity
POCP	Photochemical Ozone Creation Potential
QSAR	Quantitative Structure-Activity Relationship
RME	Reaction Mass Efficiency
RPG	Relative Process Greenness
SAR	Structure-Activity Relationship
sEF	Simple E-factor
SHE	Safety, Health, Environment
SST	Strategic science translation
tGAL	Transformation Green Aspiration Level
THF	Tetrahydrofuran
TOC	Total Organic Carbon
UK	United Kingdom
US	United States
WOE	Weight of evidence

1. INTRODUCTION

1.1. Objective of the thesis

The objective of this thesis is to provide an overlook of green chemistry metrics in organic synthesis. To begin, this thesis introduces the basic concept of green chemistry. After that, several metrics for quantifying the greenness are presented. This thesis focuses on selected metrics that are considered useful in comparing organic synthesis routes in a small laboratory scale without the use of more extensive software systems. A broader selection of green chemistry metrics has been reviewed for instance by R.A. Sheldon.[1] Complexities in quantifying "greenness" are also discussed. Finally, selected green chemistry metrics are applied in a case study comparing two different methods for synthesizing new carbon-carbon bonds (C-C); Suzuki-Miyaura coupling and palladium catalysed direct arylation.

1.2. Introduction to the subject

1.2.1. Misusing the method of science in the history of chemical pollution

History of the chemical enterprise was riddled with unintendedly perilous pollution and even intentionally suppressing information about chemical hazards. The scientific research on chemical toxicology and environmental harm remained constantly several steps behind the development of new synthetic chemicals.[2,3,4] Furthermore, Ross and Amter compiled in their US chemical industry focused book "The Polluters" a recurring pattern of "spill, stall, study" approach. Throughout history, researching the observed environmental harms or health hazards was a go-to tactic for the chemical industry to buy time and avoid regulation. In many cases the research itself was performed by biased parties.[2] Alternatively, publication of inconvenient results was either revised and altered or prevented. A prime example was the case of carcinogenic aromatic amines, namely α-naphthylamine, β-naphthylamine and benzidine, in the UK. The connection between these reagents and bladder cancer in dyestuff workers stayed successfully downplayed between 1920s and 1950s. This was achieved in collaboration by chemical industry and the government, fearing the expense of workers compensation schemes. Moreover, even after occupational cancer in the dye industry was conceded, a similar situation in the rubber industry stood censored and toned down until the 1970s.[3]

Shortcomings of the past serve as a stark reminder that good scientific practice must be maintained.

1.2.2. Emergence of green chemistry

Development of green chemistry progressed hand in hand with a changing perspective on waste management and rising environmental concerns. Around the 1970s and 1980s, environmental chemistry stayed mostly involved in identifying, measuring, supervising, and cleaning up chemical pollutants.[1] The 1990 U.S. Pollution prevention act stayed widely proposed as a milestone towards the development of green chemistry. The accepted status quo of managing waste was side-lined for the aim of preventing waste formation at the source. Paul Anastas, at the time employed by US Environmental protection agency (EPA), publicised the term "green chemistry" during 1990s.[1,5] Introduction of the 12 principles of green chemistry by P.T. Anastas and J.C. Warner in 1998 further defined what green chemistry entailed.[6,7] P.T. Anastas and J.B. Zimmermann also presented 12 principles for green engineering in 2003.[8] Anastas founded the green chemistry institute at American Chemical Society (ACS) in 1997. Royal Society of Chemistry established a journal *Green Chemistry* in 1999.[6]

2. THEORY

2.1. Green chemistry

2.1.1. The 12 principles of green chemistry – green by design

The ambition of green chemistry was to deliver a desired function while reducing use of harmful chemicals. The ideal of green chemistry would be to eventually phase out using or creating any hazardous substances. A more realistic take on developing greener chemistry, for now, is utilizing any resources as efficiently as possible while seeking alternatives to the most harmful chemicals.[1,6] The 12 principles of green chemistry, put together by Anastas and Warner, were essentially guidelines for greener reaction design. They set the starting point of planning a synthesis procedure in looking for fundamentally greener methods. The principles are presented in Table 1.[6]

Table 1. The 12 principles of green chemistry presented by P.T. Anastas and J.C. Warner rephrased.[6,7]

12 principles of green chemistry
1. Preventing waste formation instead of treating the waste
2. Maximising the use of chemicals with atom economy
3. Fewer hazardous chemicals as reactants or products in chemical synthesis
4. Designing chemicals that are less dangerous while maintaining their functional efficiency
5. Using less dangerous solvents and other intermediate materials while minimizing their use
6. Energy efficient reaction design
7. Preferring renewable raw materials when possible
8. Reducing intermediate derivates with less reaction steps or modification required to reach a desired product
9. Catalysis preferred over stoichiometric reagent use
10. Designing chemicals for safe end-of-life degradation rather than persistence
11. Monitoring processes real-time to control the formation of pollutants
12. Avoiding accidents altogether by involving chemicals with principally safer chemistry

As exhaustive as these definitions for green chemistry design were, they are not always applicable. For instance, Principle 3 is more closely defined as avoiding chemicals that risk impact on human health or environment. This might not be feasible for medicinal chemicals meant to alter human health. For these molecules,

managing them in a way that does not put them into water systems or other undue places might remain the only option.[9] Moreover, the issues green chemistry seeks to answer are complex. Consequently, a broad perspective is needed as simply transferring problems from one point to another accidentally would be counterproductive.[7,10,11]

2.1.2. Green chemistry in organic synthesis

In the case of organic synthetic chemistry, greener options are greatly needed. Synthesis of complex target molecules involves multiple reaction steps, each leaving behind unwanted side products and purification waste. R. A. Sheldon presented in 1992 an environmental factor (E—factor) that illustrated how much waste a reaction or process generated compared to the mass of obtained product. Applying the E-factor to various industry sectors showed that while the bulk chemicals industry produced on average about $1 - 5$ times more waste mass than products, for fine chemicals sector this relation was $5 - 50$ and for pharmaceuticals $25 - 100$. This stimulated attention to developing less wasteful methods, especially in the pharmaceutical synthesis.[1,12,13] Several greener synthesis processes have been designed in the industry. One example was, as discussed in further detail in chapter 3.2.2., a significantly greener synthesis procedure for sildenafil, an active ingredient in Viagra™.[1,13]

2.1.3. Criticism and barriers to green chemistry

An article by W. T. Lynch collected criticism on green chemistry. Critics suggested that it was often just a helpful "greenwashing" tool for the industry. Larger perspectives of social, political, and institutional factors were ignored, for an example interests to pursue alleviation to pollution regulations through politics rather than profoundly changing the modus operandi with greener processes.[14] Should one approach green chemistry as one more case of "spill, stall, study"[2] type of a tactic, the accusation of merely appearing more environmentally benign on one end while continuing to pollute on the other does seem plausible.[14] However, as the manifold products of the chemical industry will remain essential for humanity in the future, studies for green-by-design chemicals and manufacturing procedures do provide the most promising way forward.[15] Good, consistently applied green chemistry metrics can provide insight on how well the aim of greener procedures has been achieved or point out where the improvements are most needed.[1]

Moving on to the other side of the topic, a study by K. J. M. Matus et al. pointed out six main obstacles for green chemistry applications in the US. These obstacles might of course vary depending on location. First problem was financial as the companies were tied to their existing investments, namely their current production plants. Closing an older plant is expensive and investing in novel technologies for a new facility at the same time makes it doubly so. Second issue came with regulations that were more focused on controlling exposure to hazardous chemicals than on designing new innately safer methods. This contrast steered funds from research and development to controlling the current pollution. This provides a hard equation to solve as the current waste also needs to be taken care of responsibly. The companies needed some incentive in the game to invest in green chemistry.[16] On the other hand, increasing expense of pollution control is considered a driving motivation for applying greener technologies.[10,14,15] Thirdly, the technically complex nature of green chemistry posed a challenge. Plausible predictions on environmental impacts require expertise in multiple fields. Consequently, there was a need for conclusive databases or helpful tools to manage that vast amount of information. Furthermore, new knowledge and data needed to be gathered in the first place. The fourth and fifth obstacles were the structure and culture of a company, respectively. The final barrier was the definition of green chemistry remaining vague and hard to quantify. There was no standardised certification for a "green chemistry" product or process. The closest thing available remains the "NSF/GCI/ANSI 355: Greener Chemicals and Processes Information Standard" which simply gives a system for reporting hazards and impacts. Quantifiable green chemistry goals in a company's strategy were found helpful for better implementation.[16] Additionally, it was noted, that closing the gap on applying green chemistry depended on including it in the education of future professionals in chemistry and engineering.[15,16]

2.2. Suzuki-Miyaura coupling

Palladium catalysed Suzuki-Miyaura coupling procedure was developed around 1979 by N. Miyaura and A. Suzuki.[17] The coupling techniques were further developed and in 2010 the Nobel prize in chemistry was shared by R. Heck, E. Negishi and A. Suzuki for their work in advancing C-C bond forming reactions. Their research set the stage for current approaches in organic synthesis and served as a

muse for new synthesis methods such as palladium-catalysed direct arylation. Nowadays Suzuki-Miyaura coupling remains a commonly used synthesis method in organic chemistry. For an example, in the pharmaceutical industry it stands as one of the most applied reaction types in drug development.[18,19]

Suzuki reactions are used to create new C-C bonds between an organoboron compound and an organic halide via palladium catalyst. **Scheme 1** presents the catalytic cycle of Suzuki-Miyaura cross-coupling. The palladium (0) catalyst with a general form [Pd (0)L_2] can be achieved from either a palladium (II)- or a palladium (0) compound. The catalytic cycle proceeds through oxidative addition, transmetallation, and reductive elimination steps. In the first phase, the aryl halide and the palladium (0) catalyst form a *trans*-[ArPdXL_2] -complex by oxidative addition. (A) The next phase is called transmetallation, the *trans*-[RPdXL_2] complex forms a nucleophilic [ArPdL_2OR]-complex with the base. (B) On the other hand, the base is also involved in a reversible reaction with the organoboron compound. The [ArPdL_2OR]-complex reacts with the neutral organoboron compound forming an equilibrium of the cis- and trans- forms of a diaryl complex [ArAr`Pd$L_2$]. (C) Finally, the cis-[ArAr`PdL_2] complex undergoes a reductive elimination yielding the coupled product and a regenerated palladium catalyst. The base reacts with the trans-[ArAr`PdL_2]-complex speeding up the reductive elimination. (D)[20,21,22]
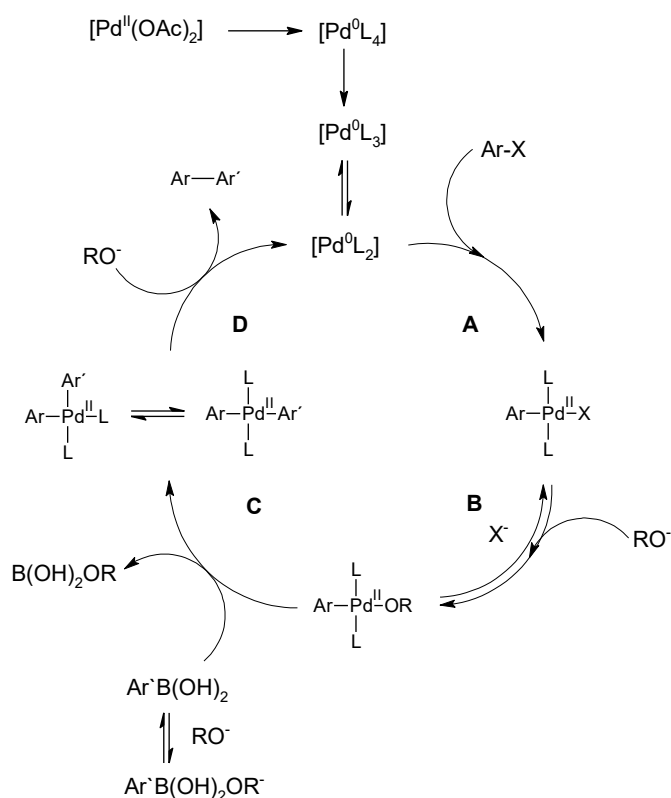
Scheme 1. The general catalytic cycle of Suzuki-Miyaura coupling (X = halide, RO⁻ =base, L =ligand).

The Suzuki-Miyaura catalytic cycle has been studied extensively. Still, the role of the base in the transmetallation step has not been fully understood even though the presence of a base has been deemed an important component in the catalytic cycle. Two possible pathways for transmetallation, named A and B, have been commonly proposed. These two routes are presented in Scheme 2. Pathway A has been suggested to proceed through a [ArPdL$_2$X]-complex and a negatively charged species [Ar`B(OH$_2$)OR⁻] while pathway B proposes a [ArPdL$_2$OR]-complex and a neutral [Ar`B(OH$_2$)] compound. The general catalytic cycle presented in Scheme 2. assumes the reaction proceeding through the pathway B.[23] In 2016 A. A. Thomas and S. E. Denmark observed experimentally a P-O-B linkage containing intermediate species that has been suggested for both pathways A and B.[24]
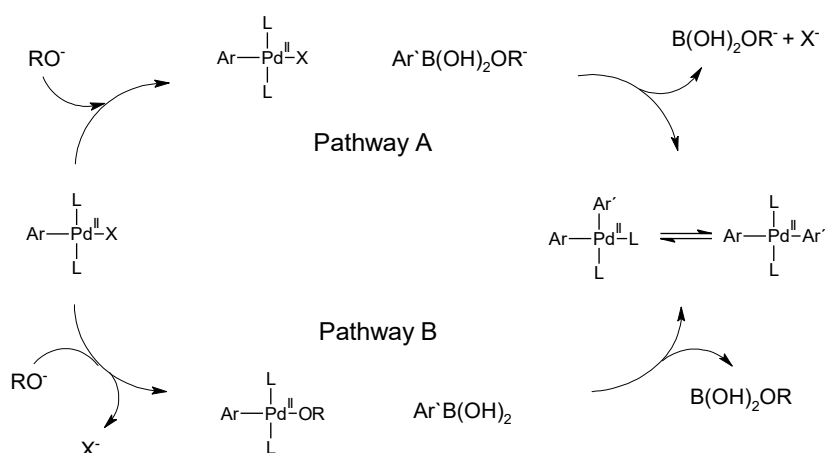
Scheme 2. The two proposed pathways for the trasmetallation step in palladium catalysed Suzuki-Miyuaura coupling.[23] (X = halide, RO⁻ =base, L =ligand)

2.3. Palladium catalysed direct arylation with added pivalic acid

In direct arylation reaction of case example presented in chapter 4, one of the two carbons intended for forming a new C-C bond was bound to a hydrogen while the other had its original bond with a halogen. Compared to using a Suzuki reaction, the direct route enables skipping the boronation step needed to acquire the organoboron starting material.[23] In the case study section of this thesis, direct coupling was conducted with the combination of a palladium catalyst and a pivalic acid co-catalyst. On the ground of experimental and computational studies it is believed that the pivalate anion lowers the energy of C-H bond cleavage and acts as a catalytic proton shuttle, transferring the leaving proton from the starting material to the carbonate base. The reaction mechanism for direct coupling is presented in Scheme 3. In the proposed mechanism, pivalate anion relocates a bromide and forms a palladium complex. A probable mechanism for the next step is Concerted Metalation-Deprotonation which gives the next intermediate through a transition state. After that there are two possible pathways for the reaction (A and B) which both result in a regenerated catalyst.[25,26] Furthermore in place of the Concerted Metalation-Deprotonation electrophilic aromatic substitution has also been proposed as a possible reaction pathway in direct arylation with palladium.[27]
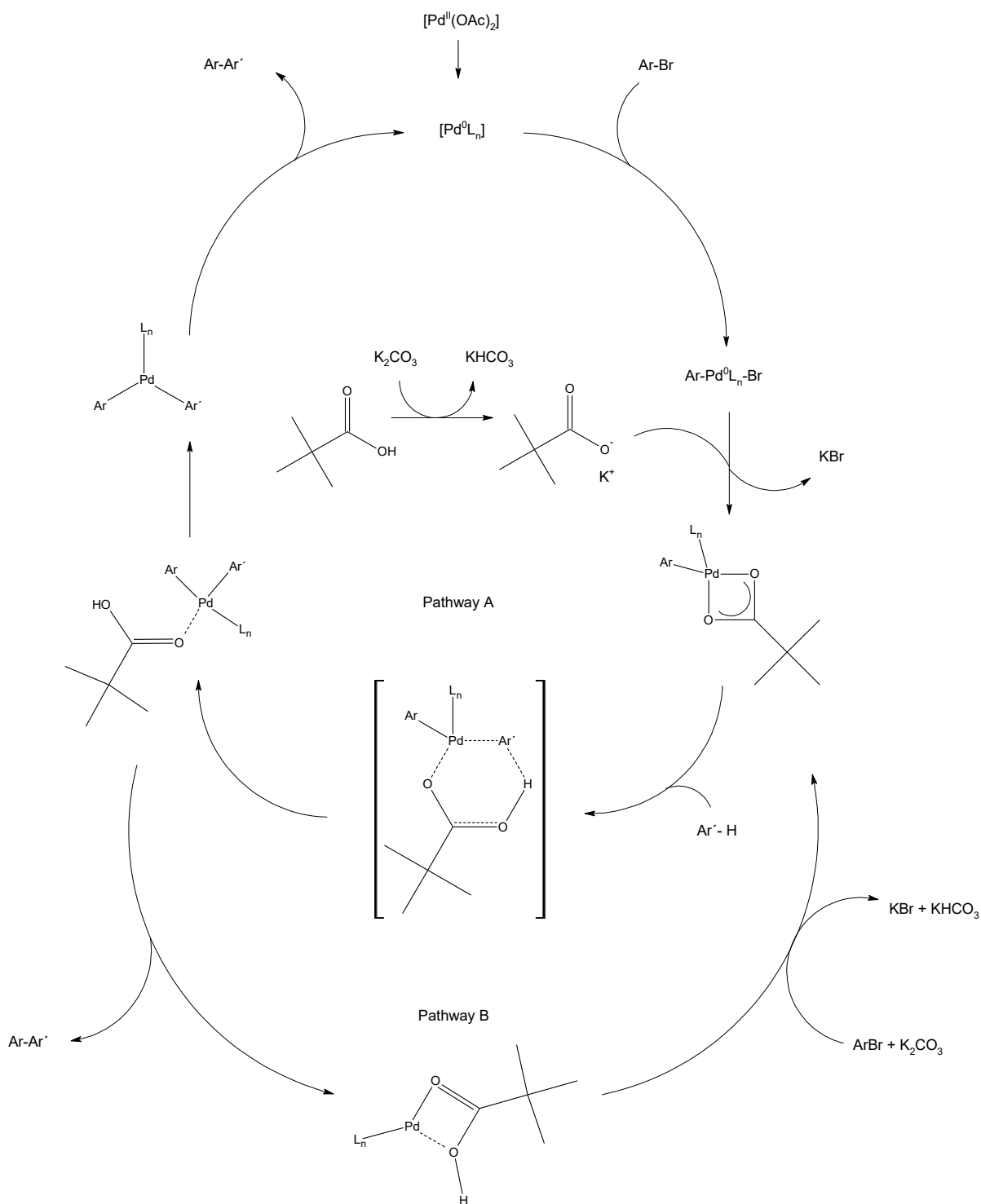
Scheme 3. Proposed pathways for the direct coupling mechanism of arenes in the presence of the pivalic acid co-catalyst (L=ligand).

2.4. Examples of reaction steps used before Suzuki-Miyaura coupling

2.4.1. Bromination with NBS

N-Bromosuccinimide (NBS) can act as a source of bromine. NBS provides a low concentration of bromine for the reaction by only giving up a Br_2 molecule when an HBr molecule is formed. The release or Br_2 from an NBS molecule is presented in Scheme 4.[28] In NBS mediated bromination reactions of materials with an aromatic ring and alkyl groups, an electrophilic aromatic substitution process was suggested to be favoured over a radical process due to the regioselectivity of bromination reactions with NBS.[29]
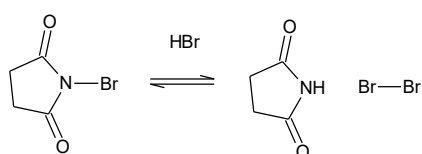
Scheme 4. NBS reacts with one HBr molecule to give one Br_2 molecule, keeping the bromine concentration in the reaction low.

2.4.2. Barbier-type borylation

Borylation using a Barbier type reaction is closely related to the Grignard reactions, but can be executed as a one-pot synthesis procedure. The reaction is air sensitive and requires an aprotic solvent. Iodine and ultrasound can be used to eliminate the unreactive magnesium oxide layer on the magnesium used in the reaction. The Barbier-type borylation is presented in Scheme 5. Magnesium reacts with an arylbromide giving the Grignard reagent. After that it is suggested that the arylmagnesiumbromide reacts with a pinacolborane reagent PinBH through a pathway that has hydridomagnesium bromide HMgBr acting as the leaving group. The HMgBr disproportionates to MgH_2 and $MgBr_2$ which can be observed as $MgBr_2$ $(THF)_4$. In the end the reaction is quenched with an acid.[30]
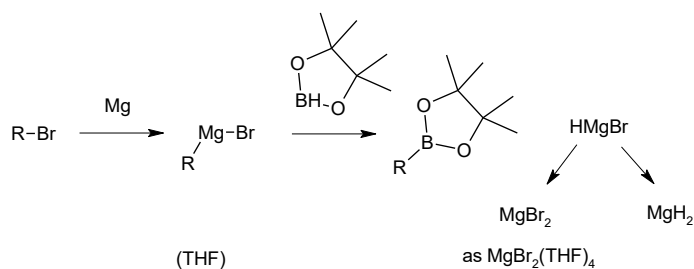
Scheme 5. The suggested pathway for the borylation reaction when HMgBr acts as the leaving group.

3. METRICS FOR QUANTIFYING GREEN CHEMISTRY

3.1. Weight of evidence (WOE) and strategic science translation (SST)

In the construction of a larger environmental risk assessment, a weight of evidence (WOE) approach is often used. The idea of a WOE method is combining diverse lines of evidence, for instance laboratory testing and community surveys, into defendable conclusions. The term WOE encompasses a wide variety of procedures and can at times be vague. US EPA has formed WOE techniques for evaluating environmental risks. One such framework divides WOE into gathering evidence, analysing the evidence, and finally weighing the body of the evidence. Different lines of evidence might vary by their reliability or relevance. Therefore, a mechanism for assigning weight to the evidence lines is needed.[31,32]

Evidence can also be used as means for political or economic strategies. In her article "Strategic Science Translation and Environmental Controversies" A. Cordner constructed a model of Strategic Science Translation (SST) based on over 110 comprehensive interviews and a year of observation in the case of contested flame-retardant chemicals. The concept of SST considered that all science interpretations are translated through the lens of a stakeholder. SST aimed to make sense of the translations and motivations of all participants and provide objective observations on controversies where the scientific conclusions of various parties differ from each other. An interpretative SST approach might for an example draw undue attention to uncertainty in the evidence, trying to emphasize its weight. This includes downplaying possibly relevant but undesirable data to claim data gaps. One example of SST interpretation A. Codner described was downplaying the environmental persistence of flame-retardant molecules. She found an example where a company´s system for chemical hazard evaluation did not include environmental persistence as a point of interest since it was an expected property in a flame-retardant molecule. However, most government and NGO´s evaluation methods do include persistence as a point of concern. Inclusion or exclusion of pollution factors in an environmental assessment, or a green chemistry metric, can affect the results significantly.[33]

3.2. Deliberations on what makes a good green chemistry metric

In the scientific literature there was a vast array of metrics seeking to define and quantify the "greenness" of a chemical reaction or process. On a larger scale that

results in a lack of direct comparability between the many different metrics. This potentially enables cherry picking between methods to control the inclusion or emphasis of different environmental factors.[10,33,34] Then again, the lack of a quantifiable standard for green chemistry is considered a discouraging factor for investing in it.[16] A new production line or process can with relative ease be proved greener in comparison to the old one. However, claims to a genuine "green chemistry product" remain hard to evaluate.[10]

An all-encompassing evaluation method for green chemistry would consider multiple criteria. It should also have a process for weighing the relevance of each criteria, preferably in a transparent manner where the relevance could be discussed and adjusted if needed.[31] A well applicable metric could also include one or few significant factors providing information about the reaction.[1] A consistent and comparable green chemistry metric should include a clearly defined baseline. This could mean for instance transparently stated measurement boundaries for the reaction or process under scope.[10] In the business of green chemistry metrics, there is an issue of too many similar metrics and no settled baselines, followed by the absence of standard approaches.[35] Also, claims of improving the greenness of a process should always be connected to a clearly defined starting point baseline.[10] Additionally, when a method is practical to apply it is more likely it is to be used.[36] Collecting the required data or the availability of the needed data might prove to be dealbreakers in the functionality of a metric.[1,13] In the following chapters a few simple mass-based metrics for evaluating the efficiency of resource are presented, also including a metric that adds reaction complexity into consideration. A couple of material safety data sheet (MSDS) data-based methods of evaluation are also introduced. Finally, a more complex life cycle analysis (LCA) approach is also considered briefly.

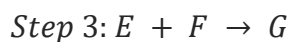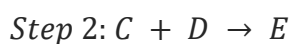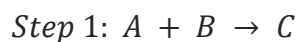## 3.3. Environmental impact calculation founded on mass

3.3.1. Atom economy

Atom economy (AE), devised by B. M. Trost around 1991[37], was one of the first green chemistry indicators. The idea of AE is also incorporated in the principle 2 of the 12 principles of green chemistry. Atom economy gives a value for the efficiency of merging the atoms of the reagent molecules to the desired final product. Unused
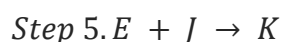
reagent atoms lower the efficiency. The general equation for atom economy is presented in Equation 1.[1,13,38]

$$AE\% \ (A \ + \ B \ + \ ... \ \rightarrow Y) = \frac{molecular \ weight \ of \ Y \times 100\%}{\sum mv \ (A, \ B, \ ...)} \tag{1}$$

Atom economy works as an atom efficiency evaluation tool for reviewing alternative reaction pathways before any experiment must be done. This makes it an easy, versatile metric commonly used in organic synthesis.[1,13] AE presented in Equation 1 is applied to individual reaction steps. Calculation the AE of a multistep process requires taking into consideration the intermediate products of each step, that are used as reagents in the next. Equation 2 presents the AE of a direct multistep process. Atom economy calculation for a diverged reaction procedure is depicted in Equation 3.[38]

$$Step \ 1: A \ + \ B \ \rightarrow \ C$$
$$Step \ 2: C \ + \ D \ \rightarrow \ E$$
$$Step \ 3: E \ + \ F \ \rightarrow \ G$$

$$AE\% \ = \frac{mw \ (G) \times 100\%}{\sum mw(A, \ B, \ D, \ F)} \tag{2}$$

$$Step \ 1. A \ + \ B \ \rightarrow \ C \qquad Step \ 3. F + \ G \ \rightarrow \ H$$
$$Step \ 2. C \ + \ D \ \rightarrow \ E \qquad Step \ 4. H \ + \ I \ \rightarrow \ J$$
$$Step \ 5. E \ + \ J \ \rightarrow \ K$$

$$AE\% \ = \frac{mw \ (K) \times 100\%}{\sum mw(A, \ B, \ D, \ F, \ G, \ I)} \tag{3}$$

Atom economy incorporates well the green chemistry idea of efficient regent usage.[1,6] However, it does not take into account the experimental yields, solvent waste or other extra chemicals not included in the stoichiometric scheme but needed to acquire the desired product.[1] In the case of organic chemicals, a similar metric of carbon efficiency (CE) is sometimes used to measure the efficiency of transferring the reagent material carbons into the final purified product. The equation for carbon efficiency is established in Equation 4.[1,13]

$$CE\% = \frac{carbon \ in \ the \ final \ product}{total \ amount \ of \ carbon \ in \ reagents} \tag{4}$$

3.3.2. E-factor

E-factor was developed by R. A. Sheldon in 1992. It concentrated on the relation of all generated process waste mass (*m*) and the final obtained product. The general E-factor is presented in Equation 5.[1,13,39]

$$E = \frac{\sum m(waste\ generated\ in\ process)}{m\ (final\ product)} \tag{5}$$

E-factor can evaluate a whole process, including all the used solvents and other chemical waste created in the production process. It is also easily applicable to multi-step processes by adding together the E-factors of all the steps. One could even calculate an E-factor for an entire company from mass of all outgoing products and involved waste streams. Soon after its introduction, E-factor was employed to compare whole chemical industry sectors and provide important information about production efficiency waste wise. The ideal E-factor for green chemistry, obviously, would be a zero.[1,9,13,39]

E-factor is at times calculated without the water used in the process, and sometimes with water included. For specification, the E-factor was split up into a simple E-Factor (sEF) and a complete E-factor (cEF). The simplified sEF leaves all solvents and water outside the equation while the cEF includes all process materials, solvents, and water. R.A. Sheldon estimates that a commercial E-factor would be something in between these two alternatives and would require the companies to collect reliable data about solvent use in the process. Usually an applied E-factor (sometimes referred to as Sheldon's E-factor) includes 10% of the solvents used and no water. This includes an assumption that, unless stated otherwise, 90% of the solvents can be recovered by distillation and used again. Equations for sEF, cEF and Sheldon's E-factor (EF) are presented in Equations 5, 6, and 7, respectively.[1,35,39]

$$sEF = \frac{\sum m(raw\ materials) + \sum m(reagents) - \sum m(product)}{\sum m(product)} \tag{5}$$

$$cEF = \frac{\sum m(raw\ materials) + \sum m(reagents) + \sum m(solvents) + \sum m(water) - \sum m(product)}{\sum m\ (product)} \tag{6}$$

$$EF = \frac{\sum m(raw\ materials) + \sum m(reagents) + 0,1 \times \sum m(solvents) - \sum m(product)}{\sum m(product)} \tag{7}$$

Recycled waste is not measured in the E-factor unless some adjustment is made, or the recycled material can be quantified and eliminated from the waste mass.[39] E-factor does not classify the created waste by how toxic, hazardous, or hard to dispose of it is.[1,13] It also fails to rule in waste that has no mass, for instance gases causing global warming or ozone layer depletion. For this purpose, Christensen et.al suggested an analogous C-factor, measuring the total mass of produced CO_2 compared to the mass of the obtained product. A C-factor could also be used as one part of a life cycle assessment (LCA) procedure.[1]

The value of E-factor is dependent on defining the boundaries of a process or reaction under scope. As mentioned in chapter 3.2., any green chemistry metric needs a specified baseline to be accurate.[10] The original E-factor by Sheldon was assuming a gate-to-gate framework.[1] Still, for an example in a pharmaceutical process, the raw material arriving to the gate might already be a highly processed molecule with several reaction steps behind it. Consequently, the E-factor for producing the advanced raw material has been outsourced. So, the question arises, who should be considered the happy "owner" of that E-factor portion? To avoid an inconsistent approach to E-factor for complex product use, Sheldon proposed a baseline of "commodity-type, commercially available, raw material" more precisely a material that was priced at the most at $100/mol for the largest possible sale quantity. In the case of Viagra™ production, one of the raw materials does not conform to this baseline definition; 1-methyl-4-nitro-3-propyl-1*H*-pyrazole-5-carboxylic acid (**1**) requires a five-step reaction process to manufacture. Should the E-factor portion of this raw material be included for Viagra™, the conventional (10% of solvents included) E-factor would jump from the originally calculated 6.4 to 13.8kg/kg, the sEF from 3.9 to 9.9 kg/kg and the cEF from 50.3 to 85.5 kg/kg. This illustrates the importance of setting a clear baseline for a green chemistry metric. The molecular structures for 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (**1**) and sildenafil (**2**) are presented in Scheme 6.[1,35] Then again, Viagra™ was also referred to as one of the success stories in green chemistry. The traditional E-factor was lowered from an original value of about 105 to 7 kg/kg by eliminating highly volatile solvents and using recovery techniques for ethyl acetate and toluene. The future aspiration for the manufacturer of Viagra™ stands at an E-factor of 4 kg/kg.[13,40]
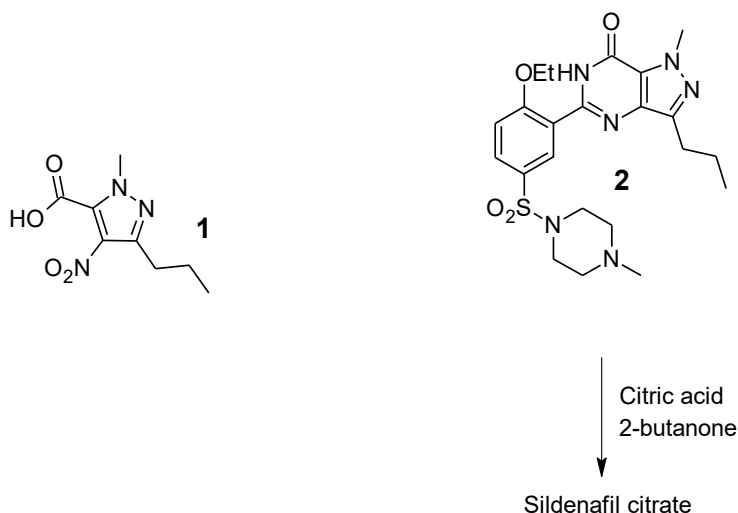
Scheme 6. The molecular structures 1-methyl-4-nitro-3-propyl-1H-pyrazole-5-carboxylic acid (**1**) and of sildenafil (**2**). Sildenafil is converted to a sildenafil citrate salt to give the final Viagra™ drug product.[1,35]

3.3.3. Process mass intensity (PMI) and reaction mass efficiency (RME)

Process mass intensity (PMI) evaluates the mass of all the materials invested in a process compared to the mass of the obtained product. It is presented in Equation 8.[1,36]

$$PMI = \frac{total\ input\ mass\ of\ materials\ in\ the\ process\ (including\ process\ H2O)}{mass\ of\ the\ obtained\ product} \qquad (8)$$

Process mass intensity was developed by the ACS Green Chemistry Institute (GCI) Pharmaceutical Round Table in 2006 by expanding on mass intensity (MI), a similar metric which excluded water usage from the equation. PMI was established as the key greenness evaluation metric for active pharmaceutical ingredients (API) and fine chemical processing in the pharmaceutical industry.[1,35,36] However, the longstanding intention was expanding to metrics leaning on a life cycle assessment (LCA) approach. The ideal PMI value would be 1, meaning that all the raw materials have been converted into a product with zero waste.[36]

Analysing PMI results from 2007 − 2008 pharmaceutical manufacturing data collected by the Green Chemistry Institute showed that the waste constitution was on average 58% solvents, 28% water, 8% raw materials and 6% other unspecified waste. However, the raw material and reagent waste are usually the most hazardous and mainly unrecyclable, and as such are a bigger issue that their percentage leads to assume.[35] PMI, like the E-factor, does not include a system for weighting the problem level of the waste for instance recyclability, toxicity or

environmental hazards.[36] Compared to the E-factor, while both are good green chemistry indicators, PMI concentrates mainly on using the resource input with the optimal efficiency while the focus of E-factor is in generating less waste.[1] On the other hand, measuring the PMI of a process is easier since it only requires data on the process input.[13,36] The PMI and E-factor can also be used together to evaluate a process. The connection between the complete E-factor and PMI is described in Equation 9.[13]

$$cEF = PMI - 1 \qquad (9)$$

One more example of a metric based on reaction input mass is reaction mass efficiency (RME). It is limited to the mass of reactants, instead of the whole process material input of PMI. Equation 10 presents the equation for RME referred to here. The more precise definition for a reactant is raw material, directly contributing to the mass of products. For instance, catalysts, ligands, and solvents are not reactants, and are therefore not considered. The idea of RME has similarities with atom economy presented in Equation 1 but it considers the masses of reagents and products, instead of the molecular weights. As such it can include both the obtained experimental yield mass, and the reaction efficiency idea of atom economy in its equation.[1,38,41]

$$RME\% = \frac{mass\ of\ product \times 100\%}{total\ mass\ of\ reactants} \qquad (10)$$

3.4. Green Aspiration level (GAL)

F. Roschangar et al. presented in 2017 a green aspiration level (GAL) method targeted for pharmaceutical manufacture process evaluation, building on their earlier developments on the method.[34,35] The method involves the complexity of a synthesis route and the E-factor (or optionally PMI). These factors are compared to the pharmaceutical industry average values that were determined by the designers of GAL. Applying the GAL to another industry or academic purpose would require defining the norm of that target group first and adjusting the tool accordingly. GAL uses Baran's Process Ideality Metric to evaluate the complexity for a synthetic process. The Ideality Metric is depicted in Equation 11. Construction reactions were defined by F. Roschangar et al. as chemical transformations yielding a molecular construction bond between two carbons or a carbon and another element. Strategic redox reactions were specified as "a type of construction reaction that directly

establish the correct functionality found in the final product and include asymmetric reductions or oxidations".[35]

$$ideality\% = \frac{no.of\ construction\ reaction\ steps + no.of\ strategic\ redox\ reaction\ steps}{no.of\ total\ reaction\ steps} \quad (11)$$

From Baran's Metric, the ideal complexity for a process is defined as presented in Equation 12.[35]

$$Complexity = ideality\% \times no.of\ all\ reaction\ steps =$$
$$no.of\ construction\ r.steps \times no.of\ strategic\ redox\ r.steps \quad (12)$$

An ideal green aspiration level for a typical mean amount chemical transformations (tGAL) was derived from Equation 13. It was first estimated using the PMI analysis materials by ASC CGI discussed in chapter 3.2.3.[35] The simplified and updated GAL of 2017 used a tGAL of 26 kg/kg.[34]

$$tGAL = \frac{E-factor\ (sEF\ or\ cEF)}{average\ complexity} \quad (13)$$

In the first step of GAL method, waste intensity is defined with either cEF (Equation 6) or PMI (Equation 8). The method sets a clear baseline for reagents included in the evaluation method. The raw materials should be priced at most in US \$100/mol (as referred to in chapter 3.2.2). F. Roschangar et al. noted that without setting the price-based starting point, their results would have lacked around 20% of the included waste. The steps of purging reactors or recycling solvents are not included in the estimation of cEF or PMI. Next GAL is calculated as presented in Equation 14.[34]

$$GAL = complexity \times 26\ kg/kg\ (tGAL) \quad (14)$$

In the final step of GAL method Relative process greenness (RPG) is obtained by dividing the green aspiration level by an E-factor. Optionally PMI (Equation 8) can also be used here to represent product vs. waste efficiency in the process. The equation for RPG is presented in Equation 15. [34,35]

$$RPG = \frac{GAL}{cEF\ (or\ PMI)} \quad (15)$$

For pharmaceutical application, the assessment framework was determined separately for each drug development phase, namely early development, late

development, and commercial use. The ranking system devised by F. Roschangar et al. is presented in Table 2.[34] The evaluation method was named Green report card and is available online for a free download. The online tool asks for development phase, complexity, sEF, and cEF. Then it calculates the RPG and provides the connected evaluation of greenness.[42]

Table 2. The "green report card" evaluation system for the RPG values obtained by GAL method as presented by F. Roschangar et al.[34]

| RPG (%) | Rating | Minimum RPG for drug development phase | | |
		Early development	Late development	Commercial
90	Excellent	109	179	248
70	Good	76	137	197
40	Average	40	67	93
	Below average	0	0	0

3.5. Waste assessed by toxicity and environmental effects

The 12 principles of green chemistry endorsed designing chemistry that was more benign to environment and human health.[6] However, mass-based green chemistry metrics like atom economy, PMI and E-factor have no inbuilt system to evaluate the toxicity of created waste.[13] Furthermore, professionals in the field of organic synthesis rarely have specified expertise in toxicology or environmental persistence of molecules. Without an easy database system provided to help, deeper estimation of the potential downstream harms caused by chemicals involved in a synthesis remains difficult.[11,16] Developing reliable predictive models for toxicity needs a huge amount of data. Examples of current data producing programs are ToxRisk in the EU and ToxCast and Tox21 programs in the US.[15,43,44] Predicting and modelling toxicity for chemicals is achieved by studying structure-activity relationships (SAR) and quantitative structure-activity relationship (QSAR) modelling.[15] Most of the green chemistry metrics presented in this chapter are based on the health, safety, and environment (SHE) data provided in the material safety data sheets (MSDS).

Safety sheets are easily available public information which makes the methods applicable for all users.

3.5.1. Environmental quotient (EQ)

The E-factor was soon after its introduction expanded with an environmental quotient (EQ) to respond the challenge of not differentiating the waste by its hazard level. A factor "Q" was added as an imprecisely defined "unfriendliness multiplier". EQ is presented in Equation 16.[1,39,45]

$$EQ = (E - factor) \times Q \qquad (16)$$

The endeavour to sensibly quantify Q inspired new green chemistry tools like EcoScale and Environmental Assessment Tool for Organic Synthesis (EATOS). These two tools were intended for synthesis evaluation in a laboratory scale. EATOS evaluates a reaction based on information available in the material safety data sheets. It considers among other things the hazard statements of chemicals (named R-phrases at the time of developing the tool) and the cost of a chemical as an indicator for the energy and reaction steps used to produce it. EATOS requires downloading a software for its use and is therefore not depicted in more detail within the scope of this thesis.[1,13,45]

3.5.2. EcoScale

EcoScale was a partially quantitative organic synthesis evaluation tool developed by Van Aken et al in 2006.[46] As mentioned earlier, it was designed for small scale use in a laboratory setting. The EcoScale score starts from 100, referring to a reaction with a 100% yield. Penalty points are taken from the ideal 100 for lower yield, dangerous chemicals, expensive reagents, complex technical setup, energy consumption, and complex purification. The simple calculation of EcoScale is presented in Equation 17. The assignment guidelines for penalty points are presented in Table 3.[1,13,46] The amounts of penalty points have been weighed to give different values to different issues with laboratory scale users in mind. Van Aken et al. noted that weighing the issues for the tool was mostly based on their professional experience and was therefore subjective. The weights are presented transparently in the penalty points and are adjustable if needed. The highest scores were given to the cumulative penalty points from dangerous chemicals.[46]

EcoScale is relatively easy to apply but it does not identify the more precise nature of the environment, health and safety hazards being scored. However, it is one of the few green chemistry tools that considers economic impact of material costs within its system. The cost of reagents also implies how complex they are and how much waste and energy their manufacture has required. The strength of EcoScale is that chemical prices and MSDS information are publicly available data.[1,13,46]

$$EcoScale = 100 - \ assigned \ penalty \ points \ (Table \ X) \tag{17}$$

Table 3. Calculation parameters for defining the penalty points in the EcoScale green metric system as presented by Van Aken et al.[46] The scale was developed to the old MSDS format, still using R-phrases, that has been since updated.[1]

Parameter	Penalty points
1. Yield	(100 - yield%)/2
2. Price of reaction components (to buy 10mmol of final product)	
Inexpensive (< $ 10)	0
Expensive ($ 10 < $ 50)	3
Very expensive (> $ 50)	5
3. Safety (based on the hazard warning symbols)	
N (danger to the environment)	5
T (toxic)	5
F (highly flammable)	5
E (explosive)	10
F+ (extremely flammable)	10
T+ (extremely toxic)	10
4. Technical setup	
Common setup	0
Instruments for controlled addition of chemicals	1
Unconventional activation technique	2
Pressure equipment, > atm	3
Any additional special glassware	1
(Inert) gas atmosphere	1
Glove box	3

5. Temperature/time	
Room temperature, < 1 h	0
Room temperature, < 24 h	1
Heating, < 1 h	2
Heating, > 1 h	3
Cooling to 0 °C	4
Cooling, < 0 °C	5
6. Workup and purification	
None	0
Cooling to room temperature	0
Adding solvent	0
Simple filtration	0
Removal of solvent with bp < 150 °C	0
Crystallization and filtration	1
Removal of solvent with bp > 150 °C	2
Solid phase extraction	2
Distillation	3
Sublimation	3
Liquid-liquid extraction	3
Classical chromatography	10

3.5.3. Greenness index

Greenness index developed by Yang Shen et al.[47] in 2016 aimed to assess the greenness of a reagent in the scope of its whole lifecycle. For this end, it considered e.g. hazards, physical properties, end-of-life disposal directions, and transporting information. The index evaluates reagents based on five different categories: health effect, general properties, odour, fire hazards, and persistence. The greenness index focuses on utilizing data available in MSDS forms since it is readily available for all users. The presented reporting format also considers the percentage of information available for the categories. The function of the index is to assess the nature of individual reagents for instance in the development phase of a reaction path. The scoring for different factors of the reagents runs from -5 to +5, the negative score being the least green option on the scale. The final score is presented as a numerical Greenness index value. The scoring system algorithm developed by Yang Shen et al. weighted the categories for relevance in a reagent's life cycle. The EcoSale-like descriptive evaluation matrix was so extensive, with 26 tables, that it

is not represented here. On the other hand, the extent of factors, compared to the EcoScale, allows for more precise knowledge on the nature of the hazards posed by an individual chemical or reagent.[47] The comprehensive Greenness index is aimed at estimating the greenness of single reagents or other chemicals intended for a reaction, while the simpler EcoScale considers an entire reaction.

3.6. Life Cycle Assessment (LCA)

Life cycle assessment (LCA) is the ambitious approach of measuring the greenness of a manufacturing process or product through the scope of its whole useful life. This ideally includes the whole cycle from procuring the raw materials and the production process itself to the end-of-life fate of the product.[1] An LCA approach consists of four steps. First comes outlining the goal for an LCA analysis and from there defining the outer limits and detail level of the assessment. Second phase is assembling all requisite data within the defined assessment scope. It is called a life cycle inventory (LCI) analysis. The third task is a life cycle impact assessment (LCIA) and fourth and final step is interpreting the results of the LCA. An LCA system includes several categories for quantifying environmental impacts. The standard ISO 14040:2006 listed as measurement points, for instance global warming potential, ozone depletion and toxicity for humans and the environment. An LCA provides the opportunity to compare in more detail the environmental effects involved in decisions between different reaction pathways and manufacturing processes.[1,36] LCA methods are used as a decision guiding tool by governments and industry both.[1]

There are still quite a few barriers to overcome for a more widely applied LCA practice. LCA is a resource demanding and laborious process. Compared to the simpler metrics like PMI or E-factor, the data gathering step is arduous. Gathering, validating, and studying reliable data for LCI requires enormous resource use. All information for the materials might not even be available at present, which is bound to affect the scope and quality of an LCA. The pharmaceutical industry especially has a limited availability of LCI data and lacks a conclusive system to evaluate the toxicity of many of the chemicals. Several companies have developed their own simplified online tools for LCA analysis. Still, there exists a need for an easily accessible, practical to use, consistent, and transparent LCA tool to be broadcasted among the entire chemical industry.[1,36]

One example of an LCA method is Fast Life Cycle Assessment of Synthetic Chemistry (FLASC) created by GlaxoSmithKline. Table 4 presents the green chemistry metrics included in the FLASC LCA analysis. It is a software intended for fast exploration of the potential greenness of different synthetic pathways in the drug development phase. It assesses the LCA of potential raw materials, "cradle-to-gate" approach and does not include the actual synthesis process. More precisely the limits include the nature of the possible reagent materials, the energy required in the production of them, and the transportation. "Depletion of oil and natural gas" in reagent material production is considered, but the same is not applied to energy generation in the scope of this LCA model.[1,48] However, the consideration for raw material production can help answer the challenge that chemical manufacturing still relies greatly on fossil fuel originated primary materials.[15]

Table 4. Green chemistry indicators in the GlaxoSmithKline's FLASC LCA analysis for reagents intended for synthetic routes.[1,48]

Green chemistry metric for LCA	Measurement unit
Total mass of input materials	kg
Energy consumption	MJ
Greenhouse gas emission equivalents	kg CO_2 equivalents
Depletion of oil and natural gas in materials production	kg
Acidification potential (AP)	kg SO_2 equivalents
Eutrophication potential (EuP)	kg PO_4^{-3} equivalents
Photochemical ozone creation potential (POCP)	kg ethylene equivalents
Total organic carbon (TOC) load before waste treatment	

4. CASE STUDY COMPARING SUZUKI-MIYAURA COUPLING AND DIRECT ARYLATION

4.1. Case study of an experiment comparing Suzuki-Miyaura reaction and direct arylation as synthetic routes

4.1.1. Synthetic procedures and the available data

Suzuki-Miyaura and direct coupling were employed as two alternative reaction path options by J.P. Heiskanen et. al. in the synthesis of benzothiadiazole cored building blocks for organic semiconductor molecules.[49] Selected synthesis routes and obtained experimental yields are depicted in Scheme 7. The direct coupling route to compound **12a** was deemed an unviable option as the final product was only obtained at highest in 33% yield due to an isomer mixture. Hence, further greenness analysis focuses solely on the synthetic path options for compound **12b**. This also illustrates that green chemistry can require customised solutions for different reactions. Determining the greenest reaction path is not always simple. All in all, J.P. Heiskanen et al. reported a total yield of 39% for the 6-step Suzuki-Miyaura route and 43% for the 4-step direct coupling path to molecule **12b**. Direct coupling is deemed a noteworthy route option when the yield for the boronation step of Suzuki-Miyaura coupling is low (here 67% yield for the compound **11b**) and when the direct arylation does not result to an inefficient isomer mixture.[49]
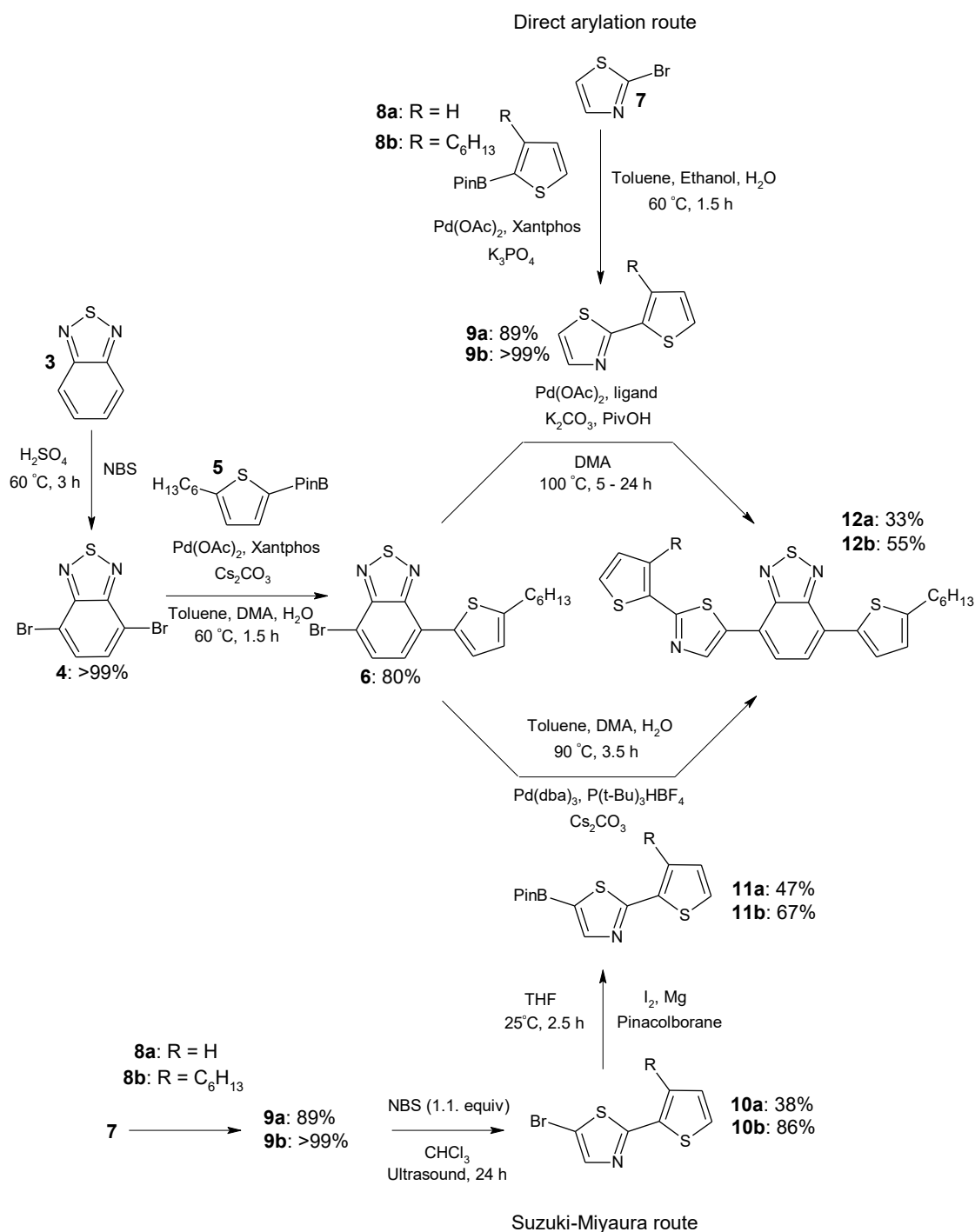
Scheme 7. Synthetic routes via Suzuki-Miyaura and direct coupling as alternative reaction path options and the obtained experimental yields, originally performed, and presented by J.P. Heiskanen et. al.[49]

The experimental section of the article by J.P. Heiskanen et al.[49] followed a general reporting format for chemical synthesis. The format is focused on depicting the procedure in a clear and reproducible manner. Used solvent amounts for purification phases, or other workup chemical amounts were not reported. The only exception

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were the solvents used in extraction phases, as there the used amounts affected the procedure and therefore had to be presented. All things considered, there is no generally accepted reporting format for including total waste amounts generated in the procedure. That being the case, of all the green chemistry metrics presented in this thesis, only atom economy, simple E-factor (sEF) and reaction mass efficiency (RME) can be calculated from the provided data in the article. Determining atom economy (Equations 1 – 3) only requires the molecular weights for the compounds. Both sEF (Equation 5) and RME (Equation 10) rely on reagent mass inputs and product mass outputs. All the chemicals used in both synthetic paths are presented in Table 5. Materials used in only the direct arylation route are depicted in Table 6 while chemicals involved in just the Suzuki reaction option are collected in Table 7. All reactions, except for the bromination ones, were carried out in protected argon atmosphere. Purification was carried out with flash chromatography.

Table 5. All the chemicals used in reaction steps and obtained yield masses that are included in Suzuki reaction and direct arylation routes both (Scheme 7), as originally presented by J.P. Heiskanen et al. in the experimental section of their publication.[49]

Step	Role	Chemical	equiv.	Amount of use (g) / (L)	(μmol)	yield
$3 \rightarrow 4$	reactant	**3**		501.1 mg	3680	1.08 g
	reactant	NBS	2.1eq.	1.358 g	7610	
	solvent (in reaction)	H_2SO_4 (97%)		5mL		
	workup	distilled water		25 mL		
	extraction	toluene		3 x 30 mL		
	drying agent	Anhydrous Na_2SO_4		n/a		

Table 5. Continued

Step	Role	Chemical	equiv.	Amount of use (g) / (L)	Amount of use (µmol)	yield
	reactant	**5**		49.2 mg	170	
	reactant	**4**	1.5eq.	75.1 mg	260	
	base	CS_2CO_3	2.5eq.	138.6 mg	430	
	catalyst	$Pd(OAc)_2$	5 mol%	1.9 mg	8.46	
	ligand	Xantphos	5 mol%	5.1 mg	8.81	
4 → 6	solvent (in reaction)	toluene		2 mL		51.1 mg
		DMA		2 mL		
		distilled water		0.5 mL		
	rinsing	SiO_2; toluene		n/a		
	purification	SiO_2; toluene 1:1 *n*-heptane		n/a		
	reactant	**7**		146.6 mg	890	
	reactant	**8b**	1.04eq	274.6 mg	930	
	base	K_3PO_4	3eq	587.4 mg	2740	
	catalyst	$Pd(OAc)_2$	2.6 mol%	5.1 mg	22.7	
	ligand	Xantphos	2.6 mol%	13.4 mg	23.2	
7 → 9b	solvent (in reaction)	toluene		3.75 mL		223.2 mg
		ethanol		1.2 mL		
		distilled water		1.2 mL		
	rinsing	SiO_2; toluene		n/a		
	purification	SiO_2; toluene		n/a		

Table 6. The chemical used in a reaction step and the obtained yield mass that is only included in the direct arylation route (Scheme 7), as originally presented by J.P. Heiskanen et al. in the experimental section of their publication.[49]

Step	Role	Chemical	Amount of use			yield
			equiv.	(g) / (L)	(µmol)	
	reactant	**6**		30.1 mg	78.9	
	reactant	**9b**	1.5eq.	30.2 mg	120	
	catalyst	Pd(OAc)$_2$	5 mol%	0.9 mg	4.0	
	ligand	Xantphos	5 mol%	2.5 mg	4.3	
	co-catalyst	PivOH	74 mol%	6.0 mg	58.7	
9b →	base	K$_2$CO$_3$	2.5eq.	27.7 mg	200	24.1
12 b	solvent (in reaction)	DMA		1 mL		mg
	rinsing	SiO$_2$; toluene		n/a		
	purification	SiO$_2$; toluene		n/a		

Table 7. All the chemicals used in reaction steps and obtained yield masses that are included only in the Suzuki reaction route (Scheme 7), as originally presented by J.P. Heiskanen et al. in the experimental section of their publication.[49]

Step	Role	Chemical	Amount of use			yield
			equiv.	(g) / (L)	(µmol)	
	reactant	**9b**		97.2 mg	390	
	reactant	NBS	1.1eq.	76.5 mg	430	
9b → 10 b	solvent (in reaction)	CHCl$_3$		6 mL		110.3 mg
	purification	SiO$_2$; toluene		n/a		

Table 7. Continued

Step	Role	Chemical	equiv.	(g) / (L)	(μmol)	yield
				Amount of use		
	reactant	**10b**		222.0 mg	670	
	reactant	pinacolborane	1.1eq.	0.11 mL	760	
	reactant	Mg	1.2eq.	20.0 mg	820	
	solvent (in reaction)	THF		6 mL		
10b → 11b	quenching	HCl		5mL		161.1 mg
	extraction	toluene		4 x 5 mL		
	drying agent	Anhydrous Na_2SO_4		n/a		
	purification	SiO_2; toluene; acetone		n/a		
	reactant	**6**		36.0 mg	94.4	
	reactant	**11b**	1.1eq.	38.4 mg	100	
	base	Cs_2CO_3	2.5eq.	79.2 mg	240	
	ligand	$P(t\text{-}Bu)_3HBF_4$	13 mol%	3.5 mg	12.1	
11b → 12b	catalyst	$Pd_2(dba)_3$	3 mol%	2.7 mg	2.9	45.2 mg
	solvent (in reaction)	toluene		1 mL		
		DMA		1 mL		
		distilled water		0.2 mL		
	rinsing	SiO_2; toluene		n/a		
	purification	SiO_2; toluene		n/a		

The Tables 5, 6 and 7 also take note of the unavailable (n/a) information that would have been relevant for rest of the metrics reviewed in this thesis. Without data on all chemical usage for the total production process, conventional E-factor (Equation 5), complete E-factor (cEF) (Equation 6) or PMI (Equation 8) cannot be applied reliably. The strength of applying the more inclusive E-factors here could have been

to point out the synthesis steps creating the most waste due to an arduous purification phase. However, this would require collecting data on all waste streams. It sounds promising to assume that less reaction steps would most likely have led to generating less waste, as the total yields for the optional synthesis routes were quite similar. However, without data on the purification procedures it remains a speculation.

4.1.2. Setting a baseline for the greenness assessment

Without a transparently and clearly stated baseline, any greenness measurement of a synthesis procedure would remain slightly arbitrary and hard to interpret.[1,10,35] Estimated price-ranges for the starting materials of experiment by J.P. Heiskanen et al.[49] were compared to the 100 $/mol baseline suggested by R.A. Sheldon[1] and F. Roschangar et al.[35] Raw material origins or prices were not originally reported.[49] Probable price-ranges for the raw materials, NBS, pinacolborane, compounds **3**, **5**, **7**, and **8b**, were scouted out from ©Merck KGaA online store.[50] Table 8 presents the listed prices for raw materials and the converted equivalent prices per one mole of substance. For all materials, the largest available quantity listed on the website, and consequently the lowest price per kilogram available online, was used for the calculations. An example of the calculations can be found in the Appendixes. The starting materials are depicted once again in Scheme 8.
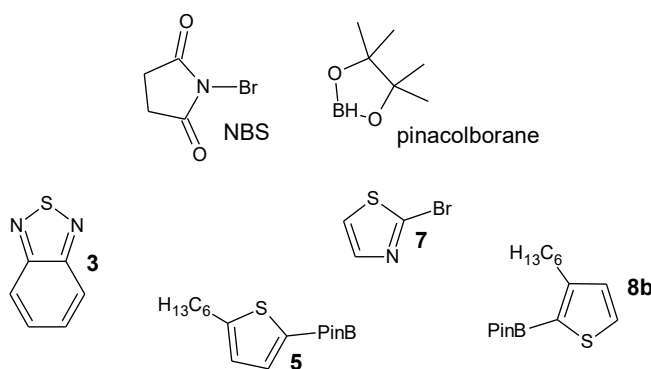
Scheme 8. The raw materials of the synthesis procedures by J.P. Heiskanen et al.[49] presented again.

Table 8. The prices for the raw material compounds were acquired from Sigma-Aldrich, from Merck online store.[50] Prices/ mol of compound were calculated for baseline comparison. J.P. Heiskanen et al. did not specify where the starting materials used in their experiments originated.[49]

Compound	Company	Product number	Purity/ concentration	Price for largest quantity	Baseline price ($/mol)
3	Sigma-Aldrich	B10900	98 %	341 $/ 100 g	474
5	Sigma-Aldrich	695629	97 %	391 $/ 5 g	23 723
7	Sigma-Aldrich	160474	98 %	117 $/ 25 g	783
8b	Sigma-Aldrich	697400	95 %	291 $/5 g	18 027
NBS	Sigma-Aldrich	B81255	99 %	125 $/ 1 kg	22
pinacolborane	Sigma-Aldrich	458945	1.0 M	210 $/ 4 x 25 mL	2100

Of all the compounds listed in Table 8, only one of them, NBS, is below the line of 100 $/ mol at 22 $/mol. Rest of the starting materials are priced significantly higher. Especially expensive were compounds **5** and **8b**, both including a pinacolborane moiety, and both priced at over ten thousand dollars per mole. The pinacolborane was also very expensive at over thousand dollars per mole. Consequently, only NBS passes for the baseline proposed by R.A. Sheldon[1] and F. Roschangar et al.[35] Still, it should be noted, without pricing data from the original article source the information assembled in Table 8 is still hypothetical. Pricing could vary with different suppliers or even be time dependent. In this thesis only one possible supplier is examined. Rates for a chemical might also depend on supply and demand factors. Wholesale prices not available online, but accessible through contacting a supplier for negotiations may possibly be cheaper than the rates listed in Table 8. All in all, F. Roschangar et al. state that while the baseline of 100 $/mol might not be agreed upon it still works to demonstrate when starting materials are notably intricate molecules to begin with.[35] All in all, the laborious step of gathering the reaction schemes for the rest of the raw materials, and counting those in, is beyond the scope of this thesis. Thus, gate-to-gate boundaries will be used for this

case example. As F. Roschangar et al. took note, exploring literature sources for synthesis paths of fine chemicals manufacturing is arduous and even then, exact references might not exist due to trade secrets.[35]

4.1.3. Atom economy calculation

The molecular weights for all the compounds used in the alternative synthesis routes to **12 b** are depicted in Table 9. The atom economies for the branched synthesis of **12b** via the Suzuki-Miyaura route and direct arylation path were determined using Equation 3. Suzuki-Miyaura reaction route is presented in Scheme 9. Direct arylation path is depicted in Scheme 10.

Table 9. Molecular weights for the compounds used or synthesised by J.P. Heiskanen et al. in the synthesis procedure presented in Scheme 7.

Compound	molecular formula	mw (g/mol)
NBS	$C_4H_4BrNO_2$	177.98406
pinacolborane	$C_6H_{13}BO_2$	127.97722
3	$C_6H_4N_2S$	136.17436
4	$C_6H_2Br_2N_2S$	293.96648
5	$C_{16}H_{27}BO_2S$	294.26038
6	$C_{16}H_{17}BrN_2S_2$	381.35358
7	C_3H_2BrNS	164.02368
8b	$C_{16}H_{27}BO_2S$	294.26038
9b	$C_{13}H_{17}NS_2$	251.41078
10b	$C_{13}H_{16}BrNS_2$	330.30684
11b	$C_{19}H_{28}BNO_2S_2$	377.37212
12b	$C_{29}H_{33}N_3S_4$	551.85242

$$3 + NBS \rightarrow 4 \qquad\qquad 7 + 8b \rightarrow 9b$$

$$\downarrow \qquad\qquad\qquad\qquad \downarrow$$

$$4 + 5 \rightarrow 6 \qquad\qquad 9b + NBS \rightarrow 10b$$

$$\downarrow$$

$$10b + \text{pinacolborane} \rightarrow 11b$$

$$6 + 11b \rightarrow 12b$$
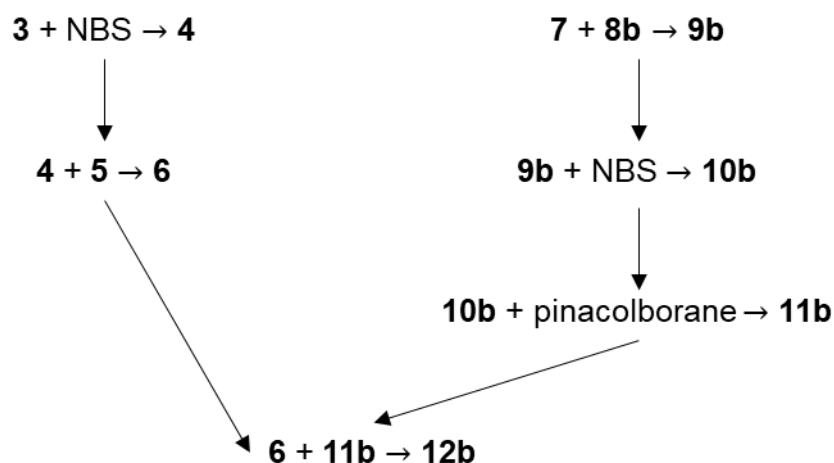
Scheme 9. The Suzuki-Miyaura route used by J.P. Heiskanen et al. to synthesize **12b**.[49]

Suzuki-Miyaura route:

$$AE\% = \frac{mw\,(\mathbf{12b}) \times 100\%}{\sum mw(\mathbf{3},\ NBS,\ \mathbf{5},\ \mathbf{7},\ \mathbf{8b},\ NBS,\ pinacolborane)} \approx 40\% \qquad (3)$$

$$3 + NBS \rightarrow 4 \qquad\qquad 7 + 8b \rightarrow 9b$$

$$\downarrow$$

$$4 + 5 \rightarrow 6$$

$$6 + 9b \rightarrow 12b$$
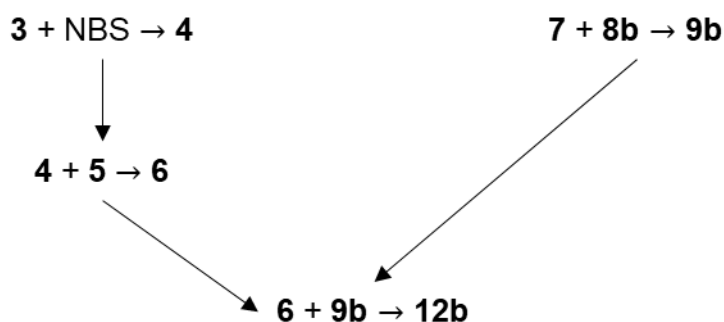
Scheme 10. The direct arylation route used by J.P. Heiskanen et al. to synthesize compound **12b**.[49]

Direct arylation route:

$$AE\% = \frac{mw\,(\mathbf{12b}) \times 100\%}{\sum mw(\mathbf{3},\ NBS,\ \mathbf{5},\ \mathbf{7},\ \mathbf{8b})} \approx 52\% \qquad (3)$$

The 6-step Suzuki route had an atom economy of 40% while the 4-step direct route had a 52% atom efficiency. From this vantage point, the direct arylation seem like the superior choice. J.P Heiskanen et al. also noted that from the atom economy point of view and timewise direct arylation was the stronger choice. However, atom

economy does not take into consideration the obtained yields. In the case of compound **12a**, that was left out of this greenness analysis, direct arylation was not a viable option due to low yield with an isomer mixture. Still, for **12b** direct arylation proved an effective choice from yield perspective.

4.1.4. Reaction mass efficiency calculation

The more precise definition of reactants used here is material that directly contributes to the mass of products formed in the reaction. For instance, catalysts, ligands, and solvents are not reactants.[41] The 6-step Suzuki Miyaura route (yield 87%) had a RME of 1,8% while the 4-step direct arylation (yield 55%) a RME of 1,0%. The longer Suzuki route has a more efficient combination of good yields and using lower stoichiometric reactant equivalents from the RME perspective. RME considers the input and output masses of the reactants.
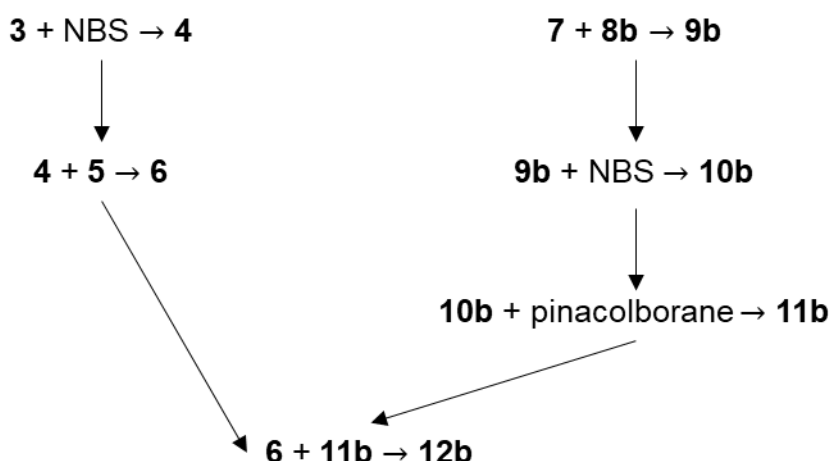
Scheme 11. The Suzuki-Miyaura route used by J.P. Heiskanen et al. to synthesize **12b**, presented again.[49]

Suzuki-Miyaura reaction route:

$$RME\% = \frac{m\,(\textbf{12b}) \times 100\%}{\sum m\,(\textbf{3},\ NBS,\ \textbf{5},\ \textbf{7},\ \textbf{8b},\ NBS,\ pinacolborane)} \approx 1.8\% \tag{10}$$

$$3 + NBS \rightarrow 4$$

$$4 + 5 \rightarrow 6$$

$$7 + 8b \rightarrow 9b$$

$$6 + 9b \rightarrow 12b$$
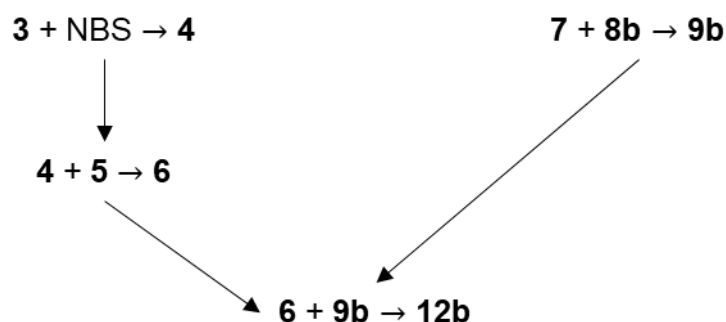
Scheme 12. The direct arylation route used by J.P. Heiskanen et al. to synthesize **12b**, presented again.[49]

Direct arylation route:

$$RME\% = \frac{m\,(\mathbf{12b}) \times 100\%}{\sum m\,(\mathbf{3},\ NBS,\ \mathbf{5},\ \mathbf{7},\ \mathbf{8b})} \approx 1.0\% \tag{10}$$

4.1.5. Simple E-factor (sEF) calculation

Simple E-factor is considered good metric for the design step of a synthesis. A total E-factor for a whole synthesis route can be calculated by simply adding the E-factors for single steps together. The experimental yields are involved in the sEF as it considers the obtained product mass.[1] The calculated sEF values, calculated according to Equation 5, for all synthesis steps of Scheme 7 are presented in Table 10. The masses for the chemicals involved in the synthesis procedure were depicted in Tables 5, 6 and 7. Examples of the calculation process can be found in the Appendixes. Simple E-factor does not include solvents or water but does include all the other reagent inputs, like the catalysts and bases, to the synthesis.

$$sEF = \frac{\sum m(raw\ materials) + \sum m(reagents) - \sum m(product)}{\sum m(product)} \tag{5}$$

Table 10. The simple E-factors calculated for all reaction steps in the synthetic routes (Scheme X) employed by J.P. Heiskanen et al.[49]

	Suzuki-Miyaura	Direct arylation
Step	sEF	sEF
3 → 4	0.72	0.72
4 → 6	4.28	4.28
7 → 9b	3.60	3.60
9b → 10b	0.57	-
10b → 11 b	1.10	-
11b → 12b	2.54	-
9b → 12 b	-	3.04
Total	12.81	11.64

The total simple E-factors of 12.81 for the Suzuki-Miyaura route and of 11.64 for the direct arylation option are quite close. This is slightly surprising, given that the Suzuki path required 2 more reaction steps compared to the direct arylation route. Even so, on this occasion the direct arylation proved a little greener an option. Additionally, given that less reactions means less time working on the synthesis of **12b**, as J.P. Heiskanen at al. pointed out.[49], direct arylation seems the superior choice at this case. However, this result illustrates the effectiveness of Suzuki-Miyaura coupling catalytic cycle with sEF of 2.54 (yield 87%), matching the 3.04 (yield 55%) of direct arylation. Yet, the final Suzuki reaction needed the sEF 0,57 bromination and sEF 1.10 borylation steps that direct arylation skipped. J.P. Heiskanen et al. pointed out that in this case the borylation of **10b** to **11b** had a relatively low yield of 67%.[49] The sEF for the reaction was relatively low at 1.0. Still, considering a similar reaction with a better yield, the sEF would probably be lower, decreasing the overall sEF score of a Suzuki route as well. The bromination reactions had the lowest sEF values, as it does not require other reagents beside NBS and in the case of compounds **4** and **10b** provided good yields. Compound **10a** on the other had had a bromination yield of only 38%.

The Suzuki reactions generated 2 − 4 times more waste that product and direct arylation around 3 times. The final Suzuki-Miyaura cycle yielding the product **12b** (yield 87%) had a much lower sEF of 2.54 compared to the earlier Suzuki cycles to **6** (yield 80%, sEF 4.28) and even **9b** (yield >99%, sEF 3.60). The Suzuki reactions

yielding compounds **6** and **9b** used the optimised catalyst/ligand system of PdoAc₂/Xantphos. The final Suzuki reaction yielding **12b** employed Pd₂(dba)₃/P(t-Bu)₃HBF₄ system. It would have been interesting to have the sEF included into the reaction optimization considerations for different catalyst/ligand systems.

4.1.6. Comparing reaction safety with a partial EcoScale analysis

None of the metrics employed above took into consideration the toxicity or environmental hazards posed by the waste or materials. A partial EcoScale[46] analysis is used to compare chemical safety in the reaction route options, Suzuki reaction and direct coupling, in the synthesis reported by J.P. Heiskanen et al.[49] Material safety data sheets were accessed in ©Merck KGaA online store.[50] Table 11 depicts again the safety part of EcoScale scoring table.[46] Tables 12, 13 and 14 present safety analysis for the reaction chemicals used by J.P. Heiskanen et al.[49] Workup and purification chemicals were not included in the assessment since EcoScale had a separate section for the workup phase. EcoScale used hazard warning symbols of chemicals as reference for the penalty points in the safety section.[46] The pictogram symbols had been updated after the publication of EcoScale. Here, the health hazard pictogram was considered to correspond toxic (T) and the skull pictogram extremely toxic (T+). Flame symbol was considered to correspond with highly flammable (F).

Table 11. Safety part of the EcoScale analysis penalty point scoring system designed by Van Aken et al. presented again.[46]

3. Safety (based on the hazard warning symbols)	Penalty points
N (danger to the environment)	5
T (toxic)	5
F (highly flammable)	5
E (explosive)	10
F+ (extremely flammable)	10
T+ (extremely toxic)	10

Table 12. Safety part´s penalty points calculated for reactions that are included in both Suzuki and direct arylation reaction paths in the reaction scheme by J. P. Heiskanen et al.[49]

Step	Hazardous chemical	Pictograms	Penalty points	Total
3 → 4	-	-	-	0
4 → 6	**4**	T+	10	25
	toluene	F, T	5 + 5	
	DMA	T	5	
7 → 9b	toluene	F, T	5 + 5	15
	ethanol	F	5	

Table 13. Safety part´s penalty points calculated for reactions that are included in only the direct arylation reaction path in the synthesis experiments by J. P. Heiskanen et al.[49]

Step	Hazardous chemical	Pictograms	Penalty points	Total
9b → 12 b	**6**	not known	-	5
	9b	not known	-	
	DMA	T	5	

Table 14. Safety part´s penalty points calculated for reactions that are included in only the Suzuki reaction path in the synthesis experiments by J. P. Heiskanen et al.[49]

Step	Hazardous chemical	Pictograms	Penalty points	Total
9b → 10 b	**9b**	not known	-	15
	CHCl$_3$	T, T+	5 + 10	
10b → 11b	**10b**	not known	-	25
	pinacolborane	F, T	5 + 5	
	Mg	F	5	
	THF	F, T	5 + 5	
11b to 12b	**6**	not known	-	15
	11b	not known	-	
	toluene	F, T	5 + 5	
	DMA	T	5	

Sum of the penalty points for the four-step direct arylation path would be 45 and for the six-step Suzuki-Miyaura rection path 95. Naturally, a longer path uses more reagents. Still, considering the hazardousness of the used reagents, in Suzuki reaction path used in the experiment by J. P. Heiskanen et al.[49] chloroform solvent and reagents in the borylation step required the use of more dangerous chemicals than the direct arylation reaction. Consequently, from toxic chemical usage point of view, the direct arylation path is the greener alternative of the two. However, the partial EcoScale analysis used in this thesis is a bit of a blunt tool. Flammable and toxic reaction elements are assigned the same weight (5 penalty points). In laboratory scale in a fume hood the flammable solvents are relatively safe to handle. On the other hand, waste that is also toxic is harder to dispose of. Still, an easy to use tool must simplify the issues under measurement. The Greenness index method described earlier provided a more comprehensive analysis of a reaction chemical.[47] Still, it was too comprehensive to be used in this thesis for analysing chemicals used in multiple reaction steps. Although a complete EcoScale analysis was not applied here, the safety penalty points were assigned a lot of weight in the total evaluation method.[46] A complete EcoScale analysis would give better insights into the relative greenness of the two synthetic paths.

4.1.7. Proposals for inclusion of green chemistry in a laboratory scale

None of the metrics employed in the preceding example chapters took into consideration the workup and purification process required before the final product **12b**, or the intermediate products can be obtained. This was due to lack of data on the used chemical amounts in the workup phase. For cEF, EF or PMI to be obtained, data of all waste streams is needed. Perhaps collecting data about the amount of generated waste could be estimated during reaction workups. In this case, the amounts of recycled solvents should also be estimated.

Calculating the simple E-factor in the development phase to assess process greenness could be interesting. sEF could provide an addition to atom economy considerations, as it includes both yield and waste generation considerations in the equation. This would keep green chemistry in the development phase as proposed by the 12 principles of green chemistry.[6] In further greenness conclusions, the question of a baseline for the metrics becomes an issue. As noted earlier in setting a baseline for this chapter's case studies, gathering reliable data on the

manufacturing process of the starting materials is challenging and time consuming. To solve this issue, F. Roschangar et al.[35] proposed mandatory green chemistry labelling for the fine chemicals industry products. Reporting for an example the complete E-factor (cEF) for product chemicals would enable a laboratory scientist to compare the greenness of reaction paths with supply chain considerations included.[35] All in all, the availability and collection of relevant data on the reactions is essential for calculating green chemistry metrics for a laboratory scale experiment.

5. CONCLUSIONS

The idea in "greening" chemistry was delivering the needed function while at the same time reducing use of harmful chemicals. The 12 principles of green chemistry offered guidelines for involving environmental and safety considerations already in a design phase of a new reaction or chemical. All in all, green chemistry remained a work in progress on many levels. It´s definition was broad, and it needed a standardised or at least a more unified approach in quantifying greenness. Currently, the green chemistry enterprise has ended up with multiple different metrics. Using different yet slightly similar metric systems with no standard baselines makes comparing greenness between various sources challenging. In the example of Viagra™ (3.2.2. E-factor), the production trend was clearly travelling to a significantly greener direction, but still different definitions for a baseline gave different quantities of E-factors for the process. Furthermore, modes of operation to gather all data required for a comprehensive greenness evaluation might not even exist yet. Historically the research of environmental or health effect of chemicals was continuously slower than the invention of new chemicals. Now with the need for new greener chemistry innovations, it would be important to have reliable methods for evaluating and comparing the greenness of different options under consideration. Green chemistry needs to be defined and quantified in greater detail. However, this is not simple as green chemistry might need to be a customised solution for every reaction and requires compromises between different dangers and harms.

This thesis considered selected metrics that could possibly prove useful in a small laboratory scale without using extensive software systems. A few of the reviewed green chemistry metrics were applied in a case study comparing Suzuki-Miyaura coupling and palladium catalysed direct arylation. These were atom economy, RME, sEF and a partial EcoScale analysis. Simple E-factor seemed like the easiest, most promising addition to use in the development phase of a new molecule or in comparing reaction path options. Using the sEF would give a green chemistry addition to the consideration of yield and time efficiency of a reaction. On a larger scale, it would be useful to have some quantified information available about the greenness of fine chemicals needed in a laboratory, as they can be already complex molecules with several reaction steps required to their manufacturing. All in all,

green chemistry was an interesting and complicated subject. It will be an important factor in helping to make future chemistry more environmentally friendly and safer.

APPENDIXES

1. Calculation example for 4.1.2. baseline prices of Table 8

An example of calculating the price/mol for compound **3** is presented. Molecular weights used for the calculations were collected in Table 9, presented with the atom economy calculation (chapter 4.1.3.). The basic equation for molar quantity (Equation 18) was used where n = amount of substance (mol), m = mass, and M = molecular weight. The multiplier 0.98 is due to the 98% purity of the product.

$$n = \frac{m}{M} = \frac{0.98 \times 100 \, g}{136.17436 \, g/mol} = 0.71966 \ldots mol \tag{18}$$

$$Price \, (\$/mol) = \frac{341 \, \$}{0.71966 \ldots mol} = 473.83 \, \$/mol$$

2. Calculation of chapter 4.1.3. Atom economy

The molecular weights were substituted to Equation 3.

$$AE\% \, (Suzuki \, route) =$$

$$\frac{551.85242 \times 100 \, \%}{136.17436 + (177.98406 \times 2) + 294.26038 + 164.02368 + 294.26038 + 127.97722}$$

$$= 40.2030 \ldots \%$$

$$AE\% \, (direct \, route) = \frac{551.85242 \times 100 \, \%}{136.17436 + 177.98406 + 294.26038 + 164.02368 + 294.26038}$$

$$= 51.7344 \ldots \%$$

3. Calculation of chapter 4.1.4. Reaction mass efficiency

The measure amount of pinacolborane (0.11 mL) was converted to milligrams with the equation for density and mass; $\rho = m \, / \, V$ where ρ = density, m = mass and V = volume. The density of pinacolborane is 0.882 g/mL.[50] Therefore the mass for 0.11 mL of pinacolborane was calculated as follows.

m (pinacolborane) = ρ × V = 0.882 g/mL × 0.11 mL = 97.02 mg

After obtaining all reactant masses, they were substituted to Equation 10.

$$RME\% \, (Suzuki \, route) = \frac{45.2 \times 100 \, \%}{501.1 + 1358 + 49.2 + 146.6 + 274.6 + 76.5 + 97.02 \, (from \, 0.11mL)}$$

$$= 1.805818 \ldots \%$$

$$RME\% \ (direct \ route) \ = \ \frac{24.1 \times 100 \ \%}{501.1 + 1358 + 49.2 + 146.6 + 274.6}$$

= 1.034555… %

4. Calculation examples to chapter 4.1.5. simple E-factor

sEF values were determined using Equation 5. The simple E-factor for step **3 → 4** was calculated as follows.

$$sEF = \frac{\sum m(raw \ materials) + \sum m(reagents) - \sum m(product)}{\sum m(product)} \tag{5}$$

$$sEF \ (\mathbf{3} \ \rightarrow \ \mathbf{4}) = \frac{501.1 \ mg + 1358 \ mg - 1080 \ mg}{1080 \ mg} \approx 0.7213888…$$

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      NBS
https://www.sigmaaldrich.com/catalog/product/aldrich/b81255?lang=en&region=US

      Pinacolborane
https://www.sigmaaldrich.com/catalog/product/aldrich/458945?lang=en&region=US

      Compound **3**
https://www.sigmaaldrich.com/catalog/product/aldrich/b10900?lang=en&region=US

      Compound **4**
https://www.sigmaaldrich.com/catalog/product/aldrich/693847?lang=en&region=US&cm_sp=Insite-_-caContent_prodMerch_cooccuranceModel-_-prodMerch10-1

      Compound **5**
https://www.sigmaaldrich.com/catalog/product/aldrich/695629?lang=en&region=US

      Compound **7**
https://www.sigmaaldrich.com/catalog/product/aldrich/160474?lang=en&region=US

Compound **8b**

https://www.sigmaaldrich.com/catalog/product/aldrich/697400?lang=en&region=US

Toluene

https://www.sigmaaldrich.com/catalog/product/sial/244511?lang=en&region=US

DMA

https://www.sigmaaldrich.com/catalog/product/sial/271012?lang=en&region=US

Ethanol

https://www.sigmaaldrich.com/catalog/product/sial/459836?lang=en&region=US

$CHCl_3$

https://www.sigmaaldrich.com/catalog/product/sial/372978?lang=en&region=US

Magnesium

https://www.sigmaaldrich.com/catalog/product/aldrich/13112?lang=en&region=US

THF

https://www.sigmaaldrich.com/catalog/product/sial/401757?lang=en&region=US