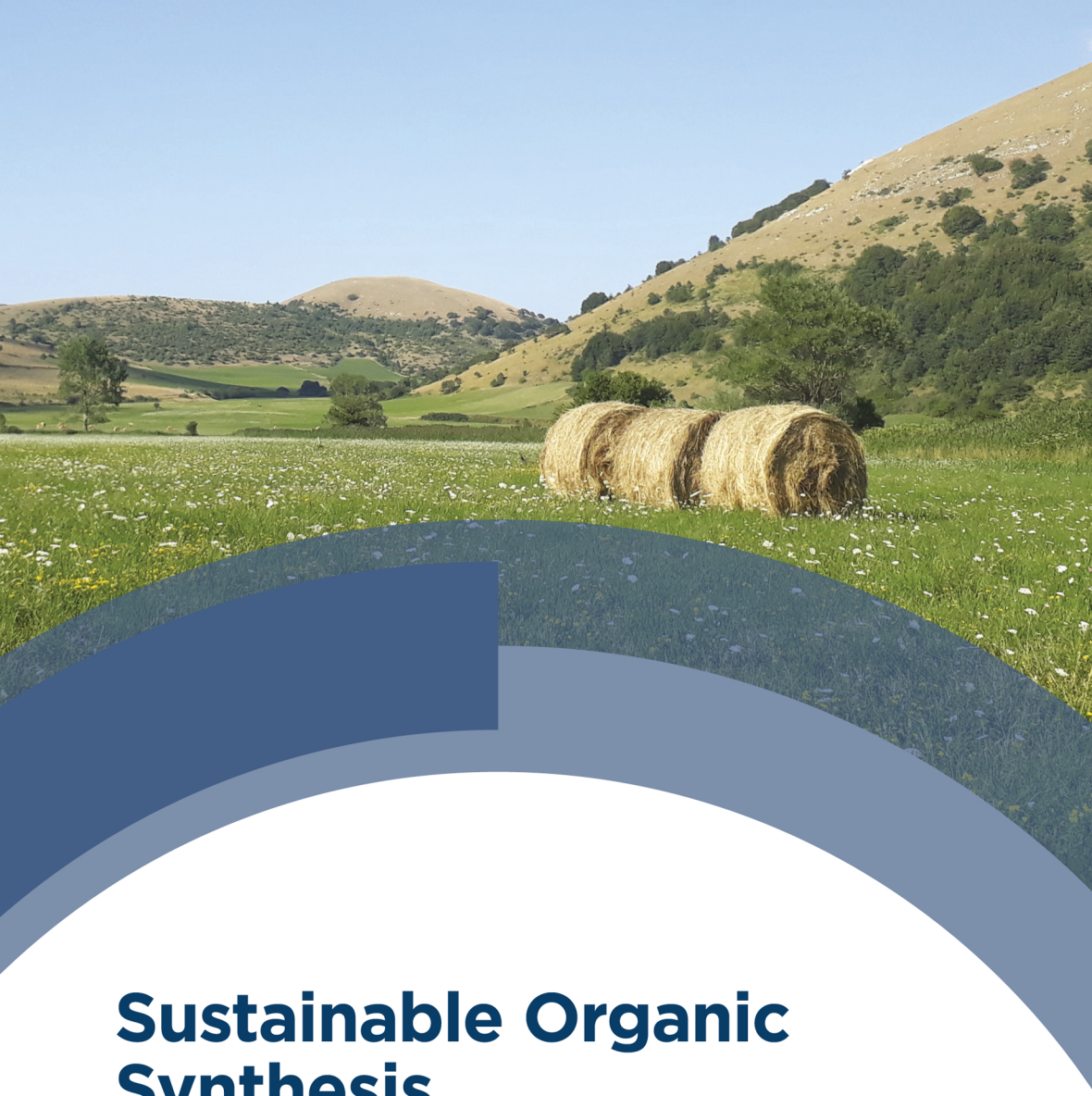

Sustainable Organic Synthesis

Tools and Strategies

Edited by Stefano Protti and Alessandro Palmieri

ROYAL SOCIETY OF CHEMISTRY

Sustainable Organic Synthesis
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Preface

Over the last sixty years, organic synthesis has reached a very high level of sophistication leading to the realization of innovative synthetic protocols for the construction of complex molecular architectures. Parallel to these achievements, new issues in today's world, dealing with the concepts of resilience (defined as *the capability and ability of an environmental system to return to a stable state after damage/disruption*),[1] sustainable development[2] and, in the case of chemical production, preventing pollution[3] have emerged.

Such issues have been levied by ordinary people to the Scientific Society, and institutions such as the International Union of Pure and Applied Chemistry (IUPAC) and the Organization for Economic Co-operation and Development (OECD) to assess the synthetic approaches in order to develop sustainable alternatives and to face this new challenge.

With the aim of spurring scientists and industries on the way to this new research philosophy, the U.S. Environmental Protection Agency, with the impregnable contribution of Paul Anastas and John Warner,[4] formalized in 1993 the concept of "Green Chemistry", as the design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances. In this regard, both guidelines (denoted as twelve principles of green chemistry)[5] and green metrics, in order to assess and quantify the environmental impact of a chemical process,[6] have been introduced and are nowadays commonly used for assessing and optimizing synthetic protocols, as well as for comparing new and old synthetic processes. In the end, this new consciousness has led scientists to explore a variety of different tools to arrive at the common goal of more sustainable chemical production. In this regard, the realization of this handbook was undertaken with the aim of providing readers with an exhaustive overview on

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Organic Green Synthesis, by covering all of the synthetic strategies that are currently adopted on the way to sustainability, corroborated also by the use of green/energy metrics.

With this purpose, the handbook is composed of three sections, namely *Activation of Chemical Substrates Under Sustainable Conditions*, *Benign Media for Organic Synthesis* and *Sustainable Approaches in Organic Synthesis*. Accordingly, the first section is focused on synthetic strategies that are well-established (including, among others, homogeneous and heterogeneous catalysis and biocatalysis), or have recently emerged (electrochemistry and visible-light photochemistry) in sustainable organic chemistry, while the second part of the handbook is devoted to bioderived and reusable solvents proposed in the literature as a sustainable alternative to VOCs as the reaction media. The aim of the third section is to describe synthetic philosophies that have recently emerged as a way of thinking to perform sustainable production. The last two chapters are finally focused to the contribution of Green Chemistry to Chemical Engineering and Industrial Chemistry. We believe that this contribution will play a key role in furnishing different practical examples to academic and industrial readers, as well as for introducing green chemistry topics to young researchers and as precious help for students.

We would like to thank the researchers that contributed to this handbook and the staff of the Royal Society of Chemistry (in particular Connor Sheppard and Helen Armes) that supported us in this project.

Alessandro Palmieri and Stefano Protti

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Biographies

Stefano Protti obtained a Master's degree in 2003 (110/110 cum laude). In 2007, he completed his PhD in Pavia focusing on photochemical arylations *via* phenyl cations. Later he moved to the LASIR Laboratory (Lille, France), where he investigated the photoreactivity and the photophysics of flavonoids. He came back to Pavia and started working in the field of (photo)green synthetic chemistry. After a postdoctoral stay at the iBitTec-S laboratory (CEA Saclay, France) carrying out studies on photocatalyzed oxidation reactions for energy storage, he moved again to Pavia. Since 2018, he has been an Associate Professor at the University of Pavia, Italy. He is currently editor of the Specialist Periodical Reports in Photochemistry of the Royal Society of Chemistry, a member of the Early Career Board of ACS Sustainable Chemistry and Engineering and of the International Advisory Board of the European Journal of Organic Chemistry. The research activity of Stefano Protti has been mainly focused on the development of new synthetic methods for the light-driven formation of C–C and C-heteroatom bonds under metal free conditions.

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Alessandro Palmieri obtained his Laurea degree *cum laude* in Chemistry in 2002 at the University of Camerino (Italy) where, five years later, he received a PhD degree in Chemical Sciences. Then, in the period 2007–2010 he held a post-doctoral fellowship and in 2008 he moved, as a visiting postdoctoral fellow, to the ITC laboratory at the University of Cambridge (Prof. Steven V. Ley). After experience as an assistant professor (2010–2013), in 2014 he was appointed associate professor in Organic Chemistry at the University of Camerino. Currently, his research interests involve (i) the chemistry of aliphatic nitro compounds, (ii) the realization of new one-pot protocols for generating and derivatizing heterocyclic systems, (iii) the preparation and use of solid supported reagents, and (iv) the development of new sustainable processes and (v) flow chemical protocols.

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Section 1

Activation of Chemical Substrates under Sustainable Conditions

CHAPTER 1

Assessing the Sustainability of Syntheses of the Anti-tuberculosis Pharmaceutical Pretomanid by Green Metrics

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1.1 Introduction

The sub-area of green metrics in the wider field of green chemistry is now a mature field of study, since the inaugural metric of atom economy was introduced in 1991.[1] Several books[2–6] and reviews[7–14] have been written on the subject, mainly focusing on the work of synthetic organic and process chemists in the pharmaceutical industry. The main purpose of introducing metrics is to provide some kind of measuring tool that can be used to gauge the reaction and synthesis efficiency with respect to input material utilization, waste production, and energy consumption of individual chemical reactions and entire synthesis plans for simple and complex target molecules. The most widely used metric among process chemists in industry that has been termed the "yardstick" by which material efficiencies of scaled-up synthesis plans are judged is process mass intensity (PMI), which is the mass ratio of

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all input materials to final target product.[15] This metric has now superseded the long-standing overall yield metric, which is the multiplicative product of all reaction yields in a synthesis plan along the longest linear branch. For convenience to the reader, Table 1.1 summarizes a brief listing of traditional metrics and their definitions that have been used by synthetic organic and process chemists to gauge reaction and synthesis performance. Generally speaking, synthesis plans that are traditionally characterized as "efficient" are ones that have the lowest possible number of reaction steps, the highest possible overall yield, a higher proportion of construction steps compared to concession or sacrificial steps, and overall high throughput and reduced process time. When it comes to counting the number of reaction steps in a synthesis plan, process chemists count the number of isolations (*i.e.*, number of purifications) of intermediate products and the final product, rather than counting the total number of chemical transformations involved as is often done for reported academic syntheses. If the number of product isolations is less than the number of chemical transformations, then the synthesis plan contains telescoped or concatenated reactions, meaning that more than one chemical transformation has taken place sequentially in a reaction vessel. Often this is done using a solvent switching technique, where the reaction solvent of the first chemical transformation is evaporated leaving behind the first crude product and a second reaction solvent is added to carry out the following chemical transformation. The second intermediate product is isolated and purified, while the first one is not. Such a strategy clearly reduces solvent demand in work-up and purification phases, particularly recrystallization and chromatographic operations. However, the strategy only works if the by-products and other impurities from the former reaction, such as excess reagents, catalysts, and other additives, do not interfere with the performance of the following one. On the other hand, if the total number of chemical transformations is the same as the number of isolations in a synthesis plan, then this implies that each intermediate product along the way, including the final product, is isolated and purified.

Despite these advances in providing quantitative measures of reaction and synthesis efficiency, the often-discussed concept of sustainability has not yet reached the same level of quantitative rigor. In fact, a recent news report in 2019 revealed the fuzzy nature of the concept and various competing definitions of it by different stakeholders, which adds to the confusion in applying the idea in a scientifically sound manner.[16] The little literature that exists on quantifying what sustainability is has mainly gravitated to thermodynamic issues and energy consumption from fossil-fuel and renewable sources.[17–26] In 2020, we decided to tackle the problem of quantifying sustainability in the context of assessing the degree of sustainability of synthesis plans from the point of view of the provenance of the input materials and energy resources used and the fate of all output materials, including waste materials and the intended final product.[27] We reasoned that since scaled-up synthesis plan design represents the core effort made by process chemists and chemical engineers, a practical definition of sustainability would have to be demonstrated

Table 1.1 Summary of traditional metrics used by synthetic organic and process chemists.

Traditional metric	Performance application	Definition	Units
Biocatalysis yield	Reaction	Ratio of mass of product to mass of biocatalyst.	$g\ g^{-1}$
Carbon efficiency	Reaction	The number of carbon atoms appearing in the target product divided by the total number of carbon atoms appearing in the reactants of a balanced chemical equation.	%
Catalyst loading	Reaction	Ratio of moles of catalyst to moles of substrate (usually the limiting reagent).	Mol%
Conversion	Reaction	Fractional amount of starting material that gets transformed or converted to all products in a chemical reaction given by $(m_{final} - m_{initial})/m_{initial}$, where the m terms refer to the masses of starting material (usually the limiting reagent) at the beginning and end of a reaction.	%
Diastereomeric excess	Reaction	If a reaction produces two diastereomers A and B, and A is the dominant diastereomer, then the diastereomeric excess is defined as the ratio $(m_A - m_B)/(m_A + m_B)$, where the m parameters refer to the masses of the respective diastereomers.	%
Effective mass yield	Reaction	Ratio of mass of product to mass of all input materials excluding aqueous materials since they are considered to be benign.	%
Enantiomeric excess	Reaction	Same definition as diastereomeric excess but referring to enantiomeric products.	%
Ideality	synthesis	Number of construction reaction steps in a synthesis that are not concession or sacrificial steps divided by the total number of reaction steps.	%
Molar efficiency	Reaction	Ratio of moles of product to sum of moles of reactants, additives, and catalysts.	%
Number of reaction steps	synthesis	Total number of chemical transformations in a synthesis along the longest branch for academic syntheses. Total number of isolations of intermediate products and final product in a synthesis for process syntheses.	Dimensionless
Overall synthesis yield	synthesis	For a linear synthesis plan, the overall yield corresponds to the multiplicative product of the individual step reaction yields. For a convergent plan, the overall yield corresponds to the multiplicative product of the individual step reaction yields along the longest branch of the synthesis plan; that is, the branch having the most number of reaction steps.	%

(*continued*)

Table 1.1 (*continued*)

Traditional metric	Performance application	Definition	Units
Process time	synthesis	The length of time elapsed to carry out a chemical reaction from the point of adding all materials to the reaction vessel to isolating the purified target product. (a) In batch operations, process time = residence time (reaction time) + workup time + purification time. Process time does not depend on reaction scale. (b) In continuous flow operations using a single tube, process time = total reaction volume/flow rate. The reaction volume is composed of the volume of reactants and the volume of reaction solvents. Process time depends on reaction scale. (c) In continuous flow operations using multiple tubes in parallel, process time = (total reaction volume/flow rate) × (1/number of parallel tubes). This operation is called numbering up or scaling out.	hours (h)
Process solvent mass intensity	synthesis	Ratio of the total mass of solvent used (excluding water) to mass of target product.	kg kg^{-1}
Process water mass intensity	synthesis	Ratio of the total mass of water used to mass of target product. The mass of water used is the difference between freshwater usage and recycled water usage.	kg kg^{-1}
Selectivity	Reaction	For a reaction producing more than one product, such as regioisomers or stereoisomers, selectivity is the ratio of mass of the desired product to the total mass of products obtained in a reaction.	%
Solvent intensity	synthesis	Ratio of total mass of solvents used (including water) to mass of target product.	kg kg^{-1}
Space-time-yield	Reaction	Ratio of mass of product to multiplicative product of total process time times total volume of input materials. Sometimes the volume of the reactor is used instead of the total volume of input materials.	kg m^{-3} h^{-1} kg m^{-3} s^{-1} kg L^{-1} h^{-1} kg L^{-1} s^{-1}
Step reaction yield	Reaction	Ratio of moles of product to moles of limiting reagent times ratio of stoichiometric coefficient of limiting reagent to stoichiometric coefficient of product.	%
Throughput	Reaction or synthesis	For reactions, it is the ratio of mass of product to reaction time. For synthesis plans, it is the ratio of mass of final target product to entire synthesis process time.	kg h^{-1}
Turnover frequency	Reaction	Ratio of turnover number to reaction time.	h^{-1}
Turnover number	Reaction	Ratio of moles of product to moles of catalyst.	Dimensionless
Yield based on recovered starting material	Reaction	A calculation of reaction yield that includes both the intended target product and unreacted starting material in a chemical reaction as the desired products; this is usually reported in papers when the true reaction yield to the intended target compound is lower than 50%.	%

according to that activity. We were successfully able to illustrate the application of a quantitative definition of sustainability to the analysis of 22 academic and industrial synthesis plans of vanillin, which is the world's most manufactured flavor ingredient. In that work, we introduced a sustainability index (SI) parameter that could be used along with PMI, sacrificial reagent (SR) consumption, input enthalpic energy (IEE) consumption, and Rowan solvent greenness index (RSGI) to provide an overall picture of efficiency and sustainability for various synthesis plans for a given target molecule. Furthermore, the set of plans could be ranked according to these five attributes using both Borda count[28,29] and poset dominance[30] methodologies. These ideas further extend our efforts to formulate a standardized framework for evaluating and reporting synthesis plan greenness, particularly in the process industry.[31] In this chapter, we apply these quantitative techniques to the analysis of four syntheses of the novel anti-tuberculosis pharmaceutical pretomanid from the common starting material 4-nitroimidazole.[32–35] We chose this compound because its synthesis plans are well documented in the literature and they are sufficiently brief that they can serve the purpose of illustrating our methodologies with minimal difficulty (see Table 1.1 for an overview).

1.2 Syntheses of Pretomanid

Pretomanid (**1**, PA-824)[1] is a candidate anti-tuberculosis pharmaceutical[36–40] developed by Pathogenesis Corporation[32] and is currently undergoing Phase III clinical trials under the direction of TB Alliance. The structure of pretomanid possesses a unique [4.3.0] fused bicyclic ring system consisting of a [1,3]-oxazinane ring (ring A) and an imidazole ring (ring B) as shown in Figure 1.1.

The four synthesis plans for this pharmaceutical under consideration in this work are shown in Schemes 1.1–1.4 corresponding to Pathogenesis (Scheme 1.1),[32] Otera (Scheme 1.2),[33] Sorensen (Scheme 1.3),[34] and Liu (Scheme 1.4),[35] respectively.

In order to maintain a fair comparison among the routes, all plans were evaluated from the same common starting material, namely 4-nitroimidazole, and all metrics were calculated based on a basis production of 1 kg of pretomanid. Scheme 1.5 shows routes to two imidazole intermediates used in the four syntheses originating from 4-nitroimidazole.

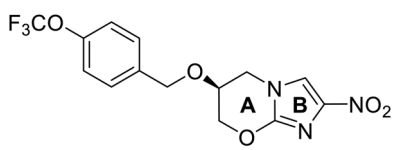
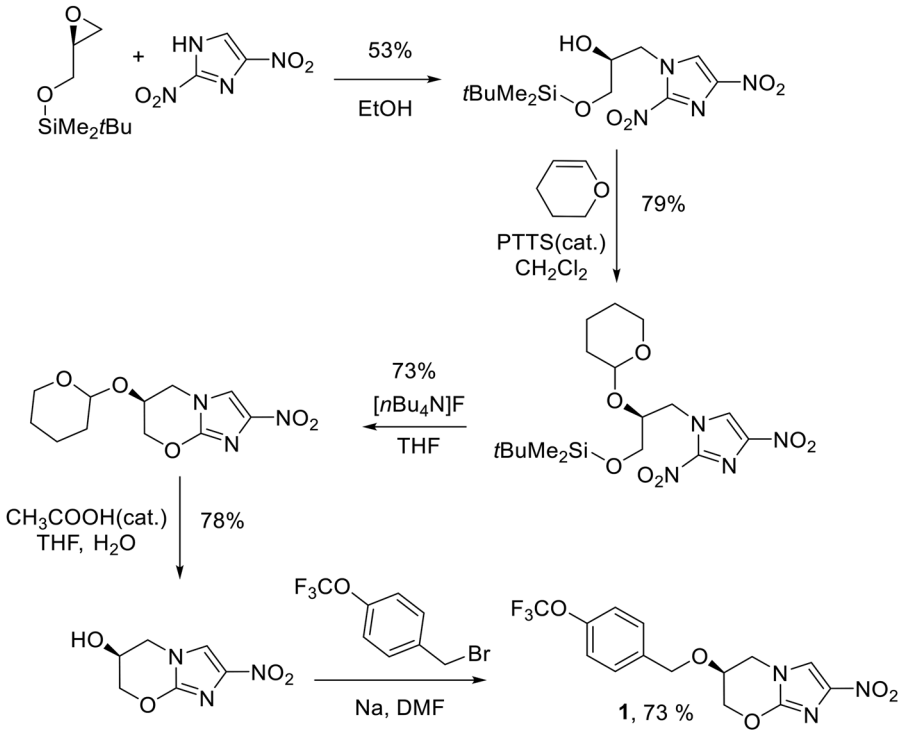
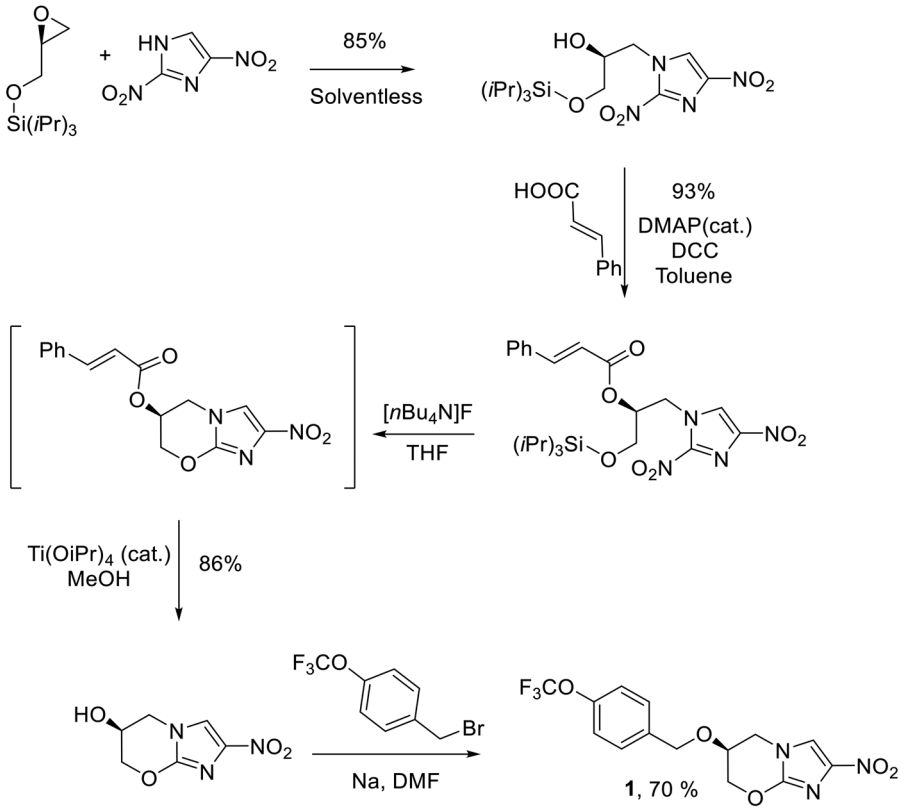


Figure 1.1 Chemical structure of pretomanid.



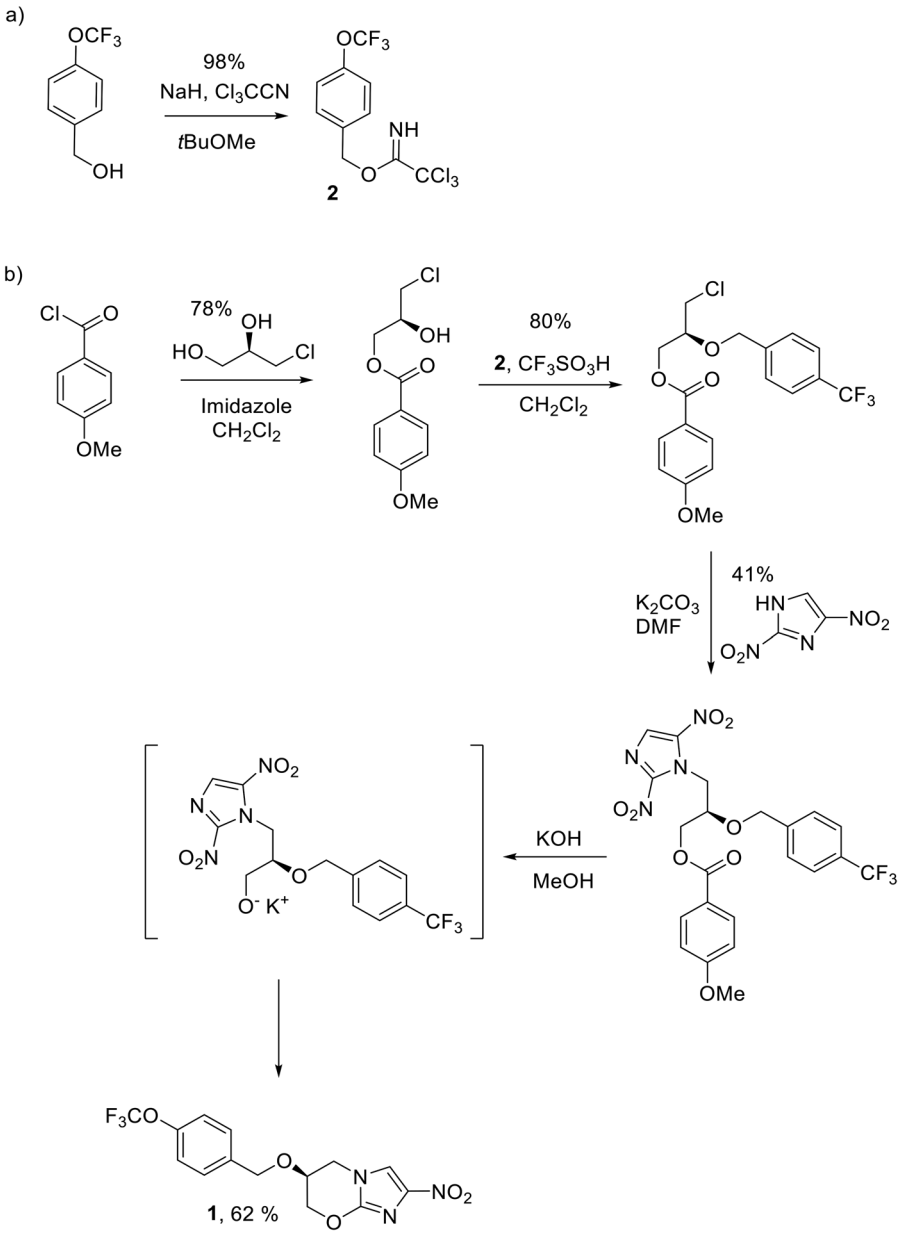
Scheme 1.1 Synthesis of pretomanid **1** by Pathogenesis (see ref. 32).

The originally discovered Pathogenesis route involves ring opening of an alcohol protected glycidol by 2,4-dinitroimidazole, followed by tetrahydropyran protection of an alcohol group, followed by ring closure and final *O*-alkylation to a bromobenzyl intermediate. The Otera route was advertised as adopting green chemistry principles, in which the authors stated that their synthesis had a reaction mass efficiency (RME) of 0.138 (or 13.8%) and consumed 258 L of reaction solvents and 46 300 L of total solvents in order to produce 1 kg of PA-824. The RME metric is the reciprocal of the PMI metric and can be expressed as a percentage, since its value is a fraction ranging between 0 and 1. These metric determinations may be directly compared with an RME of 4.1% and a consumption of 171 L of reaction solvents and 79 800 L of total solvents for the Pathogenesis route. The synthetic strategy used to build the molecule is identical to the Pathogenesis route; however, the key green attributes are that the first epoxide ring opening reaction was carried out without reaction solvent (solventless reaction) and that the synthesis was shortened by one step by telescoping two reactions so that the intermediate shown in square brackets in Scheme 1.2 was not isolated. Unlike the linear routes shown in Schemes 1.1 and 1.2,

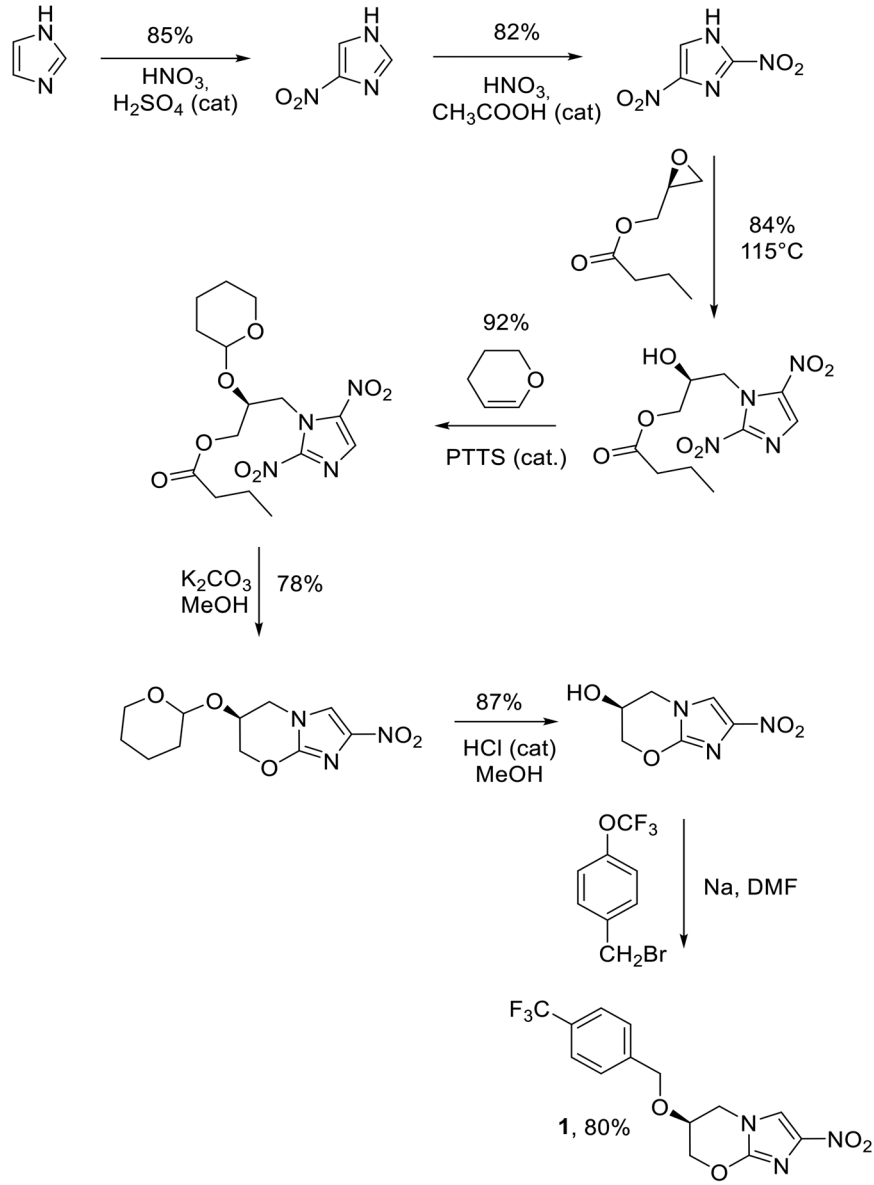


Scheme 1.2 Synthesis of pretomanid **1** by Otera and coworkers (see ref. 33).

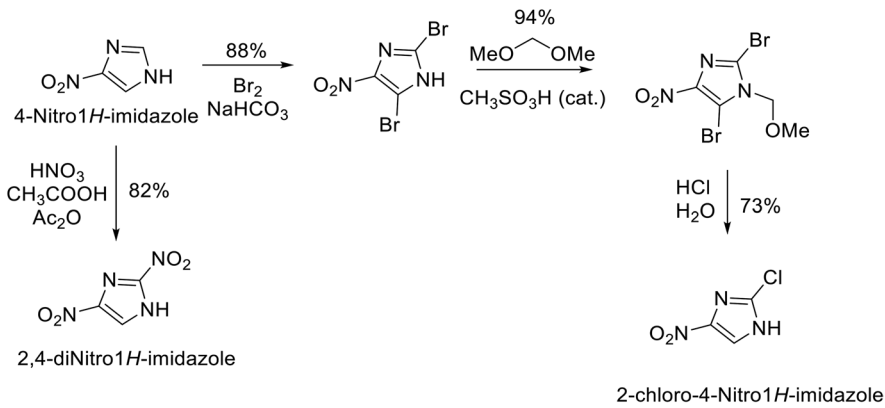
Sorensen and coworkers at Princeton University employed a convergent strategy (see Scheme 1.3) using 2-chloro-4-nitroimidazole instead of 2,4-dinitroimidazole as the starting material. The main selling point of this synthesis is that the starting imidazole did not have the same explosive properties as the dinitro derivative, thus making it a safer reagent to handle. The syntheses of 2-chloro-4-nitroimidazole and 2,4-dinitroimidazole from 4-nitroimidazole are shown in Scheme 1.5. In the Sorensen plan, one branch involves the synthesis of a trichloroethanimidate intermediate labelled as **2**. The other branch involves first esterification to form a benzoate derivative, followed by *O*-alkylation using intermediate **2**, followed by *N*-alkylation with 2-chloro-4-nitroimidazole, followed by tandem ester saponification and ring closure. Finally, Liu and coworkers invented a 7-step linear route from 4-nitroimidazole that followed closely the Pathogenesis strategy with a slight modification in the choice of protecting group in the glycidol starting material from a silyl ether to an *n*-butyl ester.



Scheme 1.3 Convergent synthesis of pretomanid **1** (parts a and b) by Sorensen and coworkers (see ref. 34).



Scheme 1.4 Synthesis of pretomanid **1** by Liu and coworkers (see ref. 35).



Scheme 1.5 Routes to various imidazole intermediates used in the four syntheses originating from 4-nitroimidazole (see ref. 40 and 41).

1.3 Sustainability Index

The sustainability index (SI)[27] for a synthesis plan is defined as the root-mean square of four fractional quantities according to eqn (1.1).

$$\mathrm{SI} = \frac{1}{2}\sqrt{\left(F_{\mathrm{VI}}\right)^2 + \left(F_{\mathrm{VO}}\right)^2 + \left(F_{\mathrm{VP}}\right)^2 + \left(F_{\mathrm{RE}}\right)^2} \tag{1.1}$$

where F_{VI}, F_{VO}, F_{VP}, and F_{RE} are the mass fraction of valorized inputs, mass fraction of valorized waste outputs, mass fraction of valorized target product, and input enthalpic energy fraction arising from renewable energy sources, respectively. Specifically, these four fractions are given by eqn (1.2)–(1.5).

$$F_{\mathrm{VI}} = \frac{M_{\mathrm{VI}}}{M_{\text{total inputs}}} = \frac{M_{\mathrm{VI}}}{M_{\mathrm{VI}} + M_{\mathrm{NVI}}} \tag{1.2}$$

$$F_{\mathrm{VO}} = \frac{W_{\mathrm{VO}}}{W_{\mathrm{VO}} + W_{\mathrm{NVO}}} \tag{1.3}$$

$$F_{\mathrm{VP}} = \frac{M_{\text{product}} - M^{*}_{\text{product}}}{M_{\text{product}}} \tag{1.4}$$

$$F_{\mathrm{RE}} = \frac{(\mathrm{IEE})_{\text{renewable}}}{(\mathrm{IEE})_{\text{total}}} \tag{1.5}$$

where M_{VI} is mass of valorized inputs, M_{NVI} is mass of non-valorized inputs, W_{VO} is waste mass of valorized outputs, W_{NVO} is waste mass of non-valorized outputs, M_{product} is mass of target product, M^{*}_{product} is mass of target product that is destined to be wasted, $(\mathrm{IEE})_{\text{renewable}}$ is the input enthalpy energy arising from renewable resources, and $(\mathrm{IEE})_{\text{total}}$ is the total input enthalpy energy obtained as a sum of all energy consumption as a result of heating and cooling over all input materials used in a synthesis plan above or below

a reference state representing the ambient temperature and pressure conditions of 298 K and 1 atm, respectively. A valorized input material is defined as one arising from renewable or recycled sources such as biomass, scrap metals, or retrieved by-products from other processes. A non-valorized input material is derived from non-renewable sources such as fossil fuels and virgin mineral ores. A valorized output material is defined as one destined to be recycled, reclaimed, or used in other processes. A non-valorized output material is defined as one that will end up as "dead waste" whether or not it undergoes treatment before release into the four main environmental compartments of air, water, soil, and sediment. The following energy sources are considered as renewable: hydroelectric, solar, wind, geothermal, and biofuels; and the following energy sources are considered as non-renewable: coal, other fossil-fuels such as petroleum and natural gas, and nuclear. According to the above mass quantities, the process mass intensity can be expressed as shown in eqn (1.6).

$$\text{PMI} = \frac{M_{\text{VI}} + M_{\text{NVI}}}{M_{\text{product}}} = \frac{M_{\text{total inputs}}}{M_{\text{product}}} \tag{1.6}$$

Based on this formalism, a given synthesis plan can therefore be said to be completely "sustainable" if the following conditions are satisfied: $F_{\text{VI}} = 1$, $F_{\text{VO}} = 1$, $F_{\text{VP}} = 1$, $F_{\text{RE}} = 1$, and SI = 1. Conversely, a given synthesis plan can be said to be completely "unsustainable" if the following conditions are satisfied: $F_{\text{VI}} = 0$, $F_{\text{VO}} = 0$, $F_{\text{VP}} = 0$, $F_{\text{RE}} = 0$, and SI = 0. Since each of the contributing fractions ranges between 0 and 1, then SI is also a fraction that can be expressed as a percentage. In the determination of SI, a number of limiting assumptions need to be made. If ethanol was used as an input material, then 10% of it was assumed to originate from renewable sources (*i.e.*, biomass) if the publication is dated after 1990, since that is the approximate time frame when biofuels were made widely available in the market. Water was considered a renewable input material due to the circulating global hydrological cycle. Mineral salts, metal-derived catalysts, and all non-aqueous and non-biologically derived materials from fossil fuels or ores were considered non-renewable inputs since their rate of renewal occurs on geological time scales that are several orders of magnitude longer than organism time scales. An arbitrary value of 0.9 was used for F_{VP} indicating that 90% of the manufactured pretomanid pharmaceutical is used as intended and 10% of it is wasted either by excretion from the human body or by shelf degradation in pharmacies. If a synthesis plan was published on or after the year 2000, $F_{\text{RE}} = 0.35$ following recent energy mix data,[43,44] and if it was published before 2000 then $F_{\text{RE}} = 0$. The cut-off year 2000 was chosen since it marked the beginning of the 21st century when ideas of sustainability began to take root in the general societal consciousness. In terms of degree of sustainability according to the definition of SI given in eqn (1.1), the Otera, Sorensen, and Liu plans are all tied at SI = 0.4823 and the Pathogenesis plan has SI = 0.4500. Table 1.2 summarizes the fractional breakdown of the contributing factors to SI for each plan. Overall, there is little differentiation between the plans based on

the two fractions F_{VP} = 0.9 (all plans), and F_{RE} = 0.35 (Liu, Otera, Sorensen) or F_{RE} = 0 (Pathogenesis) since these are set by the assumptions made. Generally, in SI analyses the greatest variation among synthesis plans arises from the F_{VI} and F_{VO} fractions. As observed in Table 1.2, the magnitudes of F_{VP} and F_{RE} significantly outweigh those of F_{VI} and F_{VO} and so their contribution to the magnitude of SI is larger. However, if reaction, work-up, and purification solvents are retrieved for re-use in the same syntheses or for entirely different syntheses, the value of F_{VO} (mass fraction of valorized outputs) dramatically increases for all plans according to the following: 0.0097 to 0.988 (Liu), 0.0010 to 0.989 (Otera), 0.0089 to 0.987 (Pathogenesis), and 0.0047 to 0.981 (Sorensen). This observation is not surprising since solvent consumption in all phases of carrying out reaction steps constitutes the bulk of materials used. In turn, the increase in F_{VO} has the effect of increasing the corresponding value of SI for each plan as shown in Table 1.3 where a 43 to 48% increase in value is calculated. The ranking of the four plans is also more spread out where the ranking order is Otera ~ Liu > Sorensen > Pathogenesis.

Table 1.4 summarizes the results of the metrics analysis based on the five attribute parameters PMI, SR, IEE, RSGI, and SI for each of the four

Table 1.2 Summary of contributing fractions for sustainability indexes determined for the four synthesis plans of pretomanid.

Plan	F_{VI}	F_{VO}	F_{VP}	F_{RE}	SI
Liu	0.0097	0.0097	0.9	0.35	0.4823
Otera	0.0023	0.0010	0.9	0.35	0.4823
Pathogenesis	0.0090	0.0089	0.9	0	0.4500
Sorensen	0.0054	0.0047	0.9	0.35	0.4823

Table 1.3 Ranking comparison of SI values upon retrieval or non-retrieval of reaction and/or chromatographic solvents.

Plan	SI (no solvent retrieval)	Rank	SI (solvent retrieval)	Rank	% Increase in SI value
Otera	0.4823	1	0.6908	1	43.2
Liu	0.4823	1	0.6904	2	43.1
Sorensen	0.4823	1	0.6880	3	42.6
Pathogenesis	0.4500	2	0.6678	4	48.4

Table 1.4 Summary of assessment parameters for an alphabetical list of the four synthesis plans for pretomanid beginning with 4-nitroimidazole.

Plan	PMI (kg kg^{-1})	SR (kg kg^{-1})	IEE (kJ kg^{-1})	RSGI (kg)	SI
Liu	15 766	24	7193	105 399	0.4823
Otera	45 276	5	18 833	313 748	0.4823
Pathogenesis	63 886	16	5730	462 158	0.4500
Sorensen	80 268	101	23 537	554 813	0.4823

pretomanid plans considered based on a production of 1 kg of the pharmaceutical from 4-nitroimidazole. PMI was determined according to eqn (1.6). The Liu plan has the lowest PMI value of 16 tonnes per kg and the Sorensen plan has the highest value of 80 tonnes per kg. In both cases, 97.5% of the PMI value arises from purification solvent consumption. The sacrificial reagent (SR) consumption parameter tracks the mass fraction of sacrificial reagents used in a synthesis plan compared to the total mass of reagents used, where sacrificial reagents are defined as those that do not contribute any atoms to the final product structure. Hence, SR is more probing than atom economy since it is directly linked with the final target bond map of the final product structure in a synthesis plan, which traces the origin of each atom back to the contributing reagent atoms and which target bonds were made in which reaction steps. Any reagents not included in this mapping are automatically classified as sacrificial. Eqn (1.7) shows the mathematical definition of SR.

$$\mathrm{SR} = \frac{\sum \text{mass sacrificial reagents}}{\sum \text{total mass reagents}} \tag{1.7}$$

Typically, sacrificial reagents are used in protecting and de-protecting group reaction steps, and oxidation and reduction reaction steps that do not contribute oxygen atoms or hydrogen atoms, respectively, toward the final target structure. Clearly, one key feature of a well-designed synthesis plan is that it maximizes its reagents consumption toward the building up of the target molecule, so that each reaction step is a target bond forming reaction. In the Pathogenesis plan (Scheme 1.1), the following sacrificial reagents were used: nitric acid (*for the synthesis of 2,4-dinitro-1H-imidazole*, see Scheme 1.5), 3,4-dihydro-2*H*-pyran (step 4), tetra-*n*-butylammonium fluoride (step 5), water (step 6), and sodium hydride (step 7). In the Otera plan (Scheme 1.2), the following sacrificial reagents were used: nitric acid (step 1), cinnamic acid and dicyclohexyldiimide (DCC) (step 4), tetra-*n*-butylammonium fluoride and methanol (step 5), and sodium hydride (step 6). In the Sorensen plan (Scheme 1.3), the following sacrificial reagents were used: bromine and sodium bicarbonate (step 1), methylal (step 2), sodium sulfite and water (step 3), *p*-methoxybenzoyl chloride and trichloroacetonitrile (step 3*), hydrochloric acid and water (step 4), potassium carbonate (step 5), and potassium hydroxide (step 6). In the Liu plan (Scheme 1.4), the following sacrificial reagents were used: dihydropyran (step 4), methanol and potassium carbonate (step 5), methanol (step 6), and sodium hydride (step 7). Among these four plans, the Otera plan utilizes the least sacrificial reagents at 5 kg per kg pretomanid and the Sorensen plan utilizes the most at 101 kg per kg pretomanid.

Based on the temperature and pressure reaction conditions for each reaction step, the input enthalpy energy (IEE) parameter tracks the enthalpic energy requirements from heating or cooling operations in the reaction, work-up, and purification phases. The largest contributor to IEE arises from heating or cooling reaction solvents since solvents constitute the bulk of the

input materials used in a synthesis plan. Among the four plans, the Pathogenesis plan utilizes the least input energy at 5700 kJ per kg pretomanid and the Sorensen plan utilizes the most at 24 000 kJ per kg pretomanid. In the Pathogenesis plan, steps 1 and 7 were carried out under cooling conditions at 0 °C and −60 °C, respectively, whereas, steps 2, 3, and 6 were carried out under heating conditions at 115 °C, 70 °C, and 45 °C, respectively. By contrast, in the Sorensen plan, steps 1, 3, 3*, 4*, and 6 were carried out under cooling conditions at 5 °C, 12 °C, 0 °C, 0 °C, and 0 °C, respectively, whereas, steps 1, 2, 4, and 5 were carried out under heating conditions at 65 °C, 40 °C, 95 °C, and 120 °C, respectively.

The Rowan solvent greenness index (RSGI)[45] quantifies the relative environmental, toxicological, and safety-hazard impacts of solvents used in reaction, work-up, and purification procedures for all reaction steps in a synthesis plan. It utilizes an overall solvent index (OSI) defined in eqn (1.8) that scales between 0 and 12 spanning the benign solvent water to the non-benign solvent benzene.

$$\mathrm{RSGI} = \sum_i m_i \left(\mathrm{OSI}_{12}\right)_i \tag{1.8}$$

where m_i is the mass of solvent i and OSI_{12} is defined as a normalized quantity over a set of solvents as shown in eqn (1.9).

$$\left(\mathrm{OSI}_{12}\right)_i = 12\left(\frac{\mathrm{OSI}_i - \mathrm{OSI}_{\min}}{\mathrm{OSI}_{\max} - \mathrm{OSI}_{\min}}\right) \tag{1.9}$$

where $\mathrm{OSI}_{\min}$ and $\mathrm{OSI}_{\max}$ are the minimum and maximum values of OSI for a set of solvents and OSI_i for a given solvent i is given by eqn (1.10).

$$\begin{aligned}\mathrm{OSI}_i = {} & 2\left(M_{\mathrm{OEL},i} + M_{\mathrm{LD50},i} + M_{\mathrm{LC50},i}\right) + M_{\mathrm{GWP},i} + M_{\mathrm{SFP},i} + M_{\mathrm{ODP},i} + M_{\mathrm{ABP},i} + M_{\mathrm{BCP},i} \\ & + M_{\mathrm{PER},i} + M_{\mathrm{soil},i} + M_{\mathrm{half\text{-}life},i} + M_{\mathrm{aqua},i} + M_{\mathrm{Q\text{-}phrase},i} + M_{\mathrm{SD},i} + M_{\mathrm{FP},i}\end{aligned} \tag{1.10}$$

where the metric parameters (M) cover occupational exposure limit (OEL, ppm), LD50 (ingestion toxicity, mg kg^{-1}), LC50 (inhalation toxicity, g m^{-3} for 4 h), global warming potential (GWP, unitless), smog formation potential (SFP, unitless), ozone depletion potential (ODP, unitless), acidity-basicity potential (ABP, unitless), bioconcentration potential (BCP, unitless), persistence potential (PER, unitless), soil sorption coefficient (soil, K_{oc}), half-life of the solvent in the environment (half-life, h), aquatic toxicity to fish (aqua, mg L^{-1} for 96 h), Q-phrase potential (Q-phrase, unitless), skin dose (SD, mg), and flash point (FP, degrees K). From eqn (1.8), it is observed that high values of RSGI can arise from high mass utilization of solvents, particularly in chromatographic purification steps (*i.e.*, high m values), as well as high impact solvents (*i.e.*, high OSI12 values). Synthesis plans that minimize solvent usage across the board and those that use benign solvents will have low overall RSGI values. Based on the RSGI metric, the Liu plan had the least solvent impact at 105 tonnes and the Sorensen plan had the most at 555 tonnes.

The most impactful solvents used in the Liu plan were chlorobenzene, acetic anhydride, dichloromethane, and dimethylformamide. In the Sorensen plan, they were hexane, dichloromethane, dimethylformamide, and methyl *t*-butyl ether. The high RSGI value in the Sorensen plan arises mainly from the large solvent consumption in the chromatographic purification operations in steps 3*, 4*, 5, and 6.

1.4 Ranking Analysis of the Pretomanid Synthesis Plans

In order to implement an unbiased ranking of synthesis plans according to various metrics, there are two well-documented methods for doing this, namely, the Borda count[28,29] method and the poset dominance[30] method. The Borda method is easy to implement and is also rapid in carrying out the computation. The poset dominance method involves a more tedious calculation but yields a more reliable result, since it considers all possible pairwise comparisons of attributes across all pairwise comparisons of synthesis plans. In the Borda count method, the plans are listed in ascending order of PMI, SR, IEE, and RSGI so that the plans having the lowest values for these attributes are ranked highest, and the plans are listed in descending order of SI so that the plans having the highest values are ranked highest. The highest score corresponds to the number of plans considered. In this case, since there are four pretomanid plans under consideration, the Borda scoring will have values of 1, 2, 3, or 4. Once these points are assigned for each attribute, the scores are tallied up and an overall Borda count is obtained for each plan. The plans are then ranked accordingly in descending order to obtain a final ranking order. Table 1.5 shows a summary of the Borda count rankings for the four pretomanid plans according to: Liu > Otera > Pathogenesis ≫ Sorensen. The Liu plan scored highest in three attributes: PMI, RSGI, and SI; whereas the Otera plan scored highest in two attributes: SR and SI. The Pathogenesis plan scored highest in only the IEE attribute, and the Sorensen plan ranked lowest in all attributes except SI.

In the poset dominance method, we first need to determine the number of pairwise attributes and the number of pairwise plan comparisons for each pairwise attribute in order to determine the overall size of the ranking exercise. Since there are five attributes, there are $5!/((5-2)!\,2!) = 10$

Table 1.5 Borda count ranking results of the four syntheses of pretomanid beginning with 4-nitroimidazole.

Plan	Borda score	Rank
Liu	17	1
Otera	16	2
Pathogenesis	14	3
Sorensen	8	4

pairwise attribute comparisons. The explicit list is as follows: PMI *versus* SR, PMI *versus* IEE, PMI *versus* RSGI, PMI *versus* SI, SR *versus* IEE, SR *versus* RSGI, SR *versus* SI, IEE *versus* RSGI, IEE *versus* SI, and RSGI *versus* SI. Since four synthesis plans are considered, there are $4!/((4-2)!\,2!) = 6$ pairwise plan comparisons that need to be made. Therefore, in total there are $10 \times 6 = 60$ pairwise comparisons that need to be made in the entire poset analysis for this illustrative example of pretomanid plans. For a given pairwise plan comparison, for a pair of attributes there are two possible outcomes: (a) a comparable pair in which plan A dominates plan B for both attributes X and Y; and (b) an incomparable pair in which plan A dominates plan B for attribute X and plan B dominates plan A for attribute Y. When a comparable pair for a given pairwise attribute comparison is found the dominant plan is identified. This sequence of steps is repeated for each pairwise attribute comparison and then the number of dominant occurrences for each plan is tallied up. As an example, if we consider the PMI *versus* SR comparison, we find that the ranking order for PMI is Liu > Otera > Pathogenesis > Sorensen and the ranking order for SR is Otera > Pathogenesis > Liu > Sorensen. The Liu *versus* Otera and Liu *versus* Pathogenesis comparisons result in incomparable pairs for both the PMI and SR attributes, *i.e.*, Liu dominates Otera for PMI but Otera dominates Liu for SR, and Liu dominates Pathogenesis for PMI but Pathogenesis dominates Liu for SR. However, the Liu *versus* Sorensen comparison results in a comparable pair since the Liu plan dominates the Sorensen plan in both PMI and SR attributes. Furthermore, the Otera plan dominates the Pathogenesis and Sorensen plans in both PMI and SR, and the Pathogenesis plan dominates the Sorensen plan in both PMI and SR. As a result of these pairwise comparisons, the Liu plan is assigned 1 dominance, the Otera plan is assigned 2 dominances, the Pathogenesis plan is assigned 1 dominance, and the Sorensen plan is assigned a 0 dominance. Table 1.6 summarizes the results of the 60-pair poset dominance analysis for the four pretomanid plans where the overall ranking order is as follows: Otera = Liu > Pathogenesis $\gg$ Sorensen. We observe that both ranking methods essentially give the same ranking result, since there is only a one-point difference between the Otera and Liu methods in the Borda count method compared to identical points in the poset method.

Table 1.6 Poset ranking results of the four syntheses of pretomanid beginning with 4-nitroimidazole.

Plan	Poset dominances	Rank
Otera	12	1
Liu	12	1
Pathogenesis	7	2
Sorensen	0	3

1.5 Conclusion

In this chapter, we have illustrated how process mass intensity (PMI), sacrificial reagent (SR) consumption, input enthalpic energy (IEE) consumption, Rowan solvent greenness index (RSGI), and sustainability index (SI) based on valorized input and output materials and fraction of renewable energy consumption can be used to evaluate overall synthesis plan greenness. Based on these five key attributes, it is possible to rank synthesis plans in an unbiased way by using Borda count or poset dominance analysis. In this illustrative example of four pretomanid syntheses beginning from the same starting material, we find that the Otera plan's claim to follow green chemistry principles is supported by the present quantitative analysis. We also have shown that the competing plan documented by Liu and coworkers is also highly ranked. Further improvements to the synthesis of this pharmaceutical are always possible and such plans can be evaluated by the same methodology described in this work, provided that full disclosure of their plan details is made. The sustainability index determined from input provenance and output fate is sensitive to various assumptions in the determination of the four contributing fractions and hence its reliability is strongly governed by the availability of detailed experimental procedures, and thermodynamic (temperature dependent heat capacity functions for substances and equation of state data), toxicological, and safety-hazard parameters for all materials involved. The most challenging contributing mass fraction to SI to determine is FVP, since there are no repository databases that keep track of each chemical commodity's fate once it is produced by any sector of the chemical industry. Nevertheless, the evaluation of SI is straight forward, and it is hoped that it will find use among process chemists to evaluate their plans according to green chemistry principles in a more rigorous, robust, and convincing way.

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CHAPTER 2

Homogeneous Catalysis

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2.1 Introduction

The rapid growth of the human population has caused a high impact on the planet, resulting in the depletion of its resources and an increase in pollution. This fact is threatening the environment and causing health issues; therefore, more sustainable development is required. In 1987, the World Commission on Environment and Development stated that "*sustainable development should meet the needs of the present without compromising the ability of future generations to meet their own needs*".[1] Sustainable chemistry can be defined as one which: "*should use resources, including energy, at a rate at which they can be replaced naturally, and the generation of waste cannot be faster than the rate of their remediation*".[2] In this context, green chemistry emerged in the 1980s focusing on the elimination of the wastes generated by the industrial sector to minimise pollution of the environment.[3,4] Therefore, it is desired

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that chemicals, reactions and processes are both sustainable and green at the same time when developing new synthetic methodologies.

Green chemistry is defined as the "*design of chemical products and processes that reduce or eliminate the use and generation of hazardous substances*".[5] Green chemistry aims at the efficient utilization of (preferably renewable) raw materials, and the elimination of waste, toxic and/or hazardous reagents and solvents in the manufacture and application of chemicals. This can be achieved by meeting the Twelve Principles of Green Chemistry in the development of new synthetic methodologies.[6]

1. It is better to prevent waste than to treat or clean up waste after it is formed.
2. Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.
3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.
5. The use of auxiliary substances (*e.g.* solvents, separation agents *etc.*) should be made unnecessary wherever possible and innocuous when used.
6. Energy requirements should be recognized for their environmental and economic impact and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.
7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.
8. Unnecessary derivatization (blocking group, protection/deprotection, temporary modification of physical/chemical processes) should be avoided whenever possible.
9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.
11. Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. Substances and the form of a substance used in a chemical process should be chosen so as to minimise the potential for chemical accidents, including releases, explosions and fires.

Green metrics provide important indicators to measure how green a process is. Although several metrics have been proposed, such as Reaction Mass Efficiency (RME) or Process Mass Intensity (PMI), the E-factor (environmental factor) and the Atom Economy (A. E.) are the most widely used.

The E-factor, defined as the mass of waste generated per mass of product (Eqn (2.1)),[7] is used to evaluate the amount of waste generated per kg of product synthesised in a chemical process.[8]

$$E = \frac{\text{Mass of waste (kg)}}{\text{Mass of final product (kg)}} \tag{2.1}$$

The table of E-factors for chemical industries (see Table 2.1) was published in 1992[9] and encourages fine chemical and pharmaceutical industries to reduce the quantity of waste generated in their processes. This is because the synthesis of fine chemicals and pharmaceuticals usually involves multi-step and stoichiometric syntheses rather than catalytic processes.

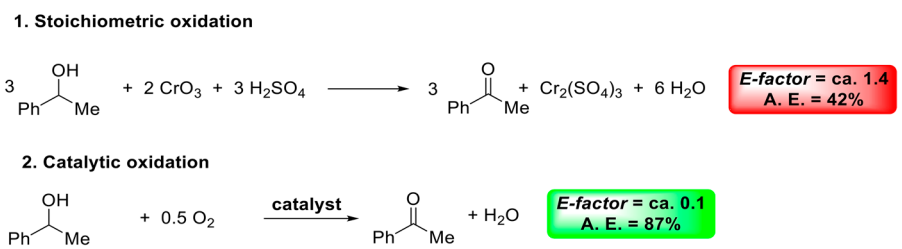
Another important factor to consider is the atom economy, which is calculated by dividing the molecular weight of the final desired product by the sum of the molecular weights of all chemical precursors, and expressed as a percentage (Eqn (2.2)).[10] Atom economy addresses the question of selectivity in organic chemistry and it is an important parameter in order to evaluate the amount of waste that can be generated.

$$\text{A. E.} = \frac{\text{Molecular weight of product}}{\text{Molecular weights of reagents}} \times 100 \tag{2.2}$$

It is expected that the E-factor and the A. E. are close to 0 and 100% respectively for a sustainable synthetic methodology. As can be seen in Scheme 2.1, the use of a catalyst has a huge impact on the E-factor and the A. E. in the oxidation reaction of 1-phenylethan-1-ol. The E-factor of *ca.* 0.1 and the A. E. close to 90% assures the development of more sustainable processes by the use of catalysis.

Table 2.1 E-Factors for chemical industries.

Industry sector	Tonnage	E-Factor (kg waste/kg product)
Oil refining	10^6–10^8	<0.1
Bulk chemicals	10^4–10^6	<1–5
Fine chemicals	10^2–10^4	5 to >50
Pharmaceuticals	10–10^3	25 to >100



Scheme 2.1 Atom economies and E-factors for the stoichiometric and catalytic oxidation of 1-phenylethan-1-ol.

In recent decades, life cycle assessment (LCA) has emerged as a method for evaluating the environmental impact of a chemical product.[11–13] LCA not only analyses the extraction of the raw material and the production of the chemical product, which is known as cradle-to-gate analysis, but the whole life cycle of a product or process, from the extraction of raw materials to production, distribution, use and disposal or recycling of the product, which is known as cradle-to-grave analysis.

2.2 Catalysis

One of the major sources of waste generation is the use of stoichiometric reagents in organic synthesis, such as stoichiometric oxidations and reductions or the use of Lewis and Brønsted acids or bases in classical chemical syntheses. Therefore, it is required to shift from stoichiometric reactions with low atom economy and high E-factor to catalytic processes in which the amount of waste generated is minimised. A representative example could be the use of sustainable H_2, produced *via* water splitting using renewable electricity, in reduction reactions and in the presence of a catalyst instead of using stoichiometric amounts of $NaBH_4$ as a hydrogen source. In this scenario, no metal salts would be generated as by-products.

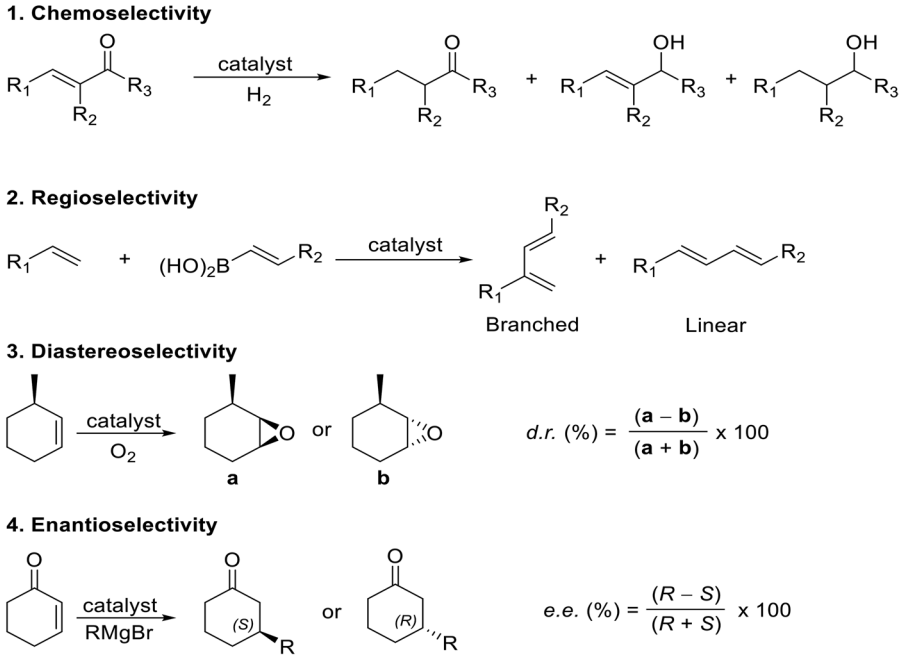
The term catalyst is defined by the IUPAC as "*a substance that increases the rate of a reaction without modifying the overall standard Gibbs energy change in the reaction; the process is called catalysis. The catalyst is both a reactant and product of the reaction*".[14] Two important parameters to evaluate the catalytic activity are the turnover number (TON) and turnover frequency (TOF) (Eqn (2.3) and (2.4)). The turnover number measures the number of turns of a catalytic cycle and is defined as the number of moles of products that a catalyst produces per mole of catalyst. On the other hand, the turnover frequency is the number of catalytic cycles in a specific time period.

$$\text{TON} = \frac{\text{mol product}}{\text{mol catalyst}} \tag{2.3}$$

$$\text{TOF} = \frac{\text{TON}}{\text{time (h)}} \tag{2.4}$$

A catalyst not only increases the reaction rate but can also direct the reaction to yield a certain product. Selectivity is one of the most important factors to control in catalysis since a subtle change in the catalyst may have a big influence on its selectivity. Different types of selectivity can be present in a chemical transformation (Scheme 2.2):[15]

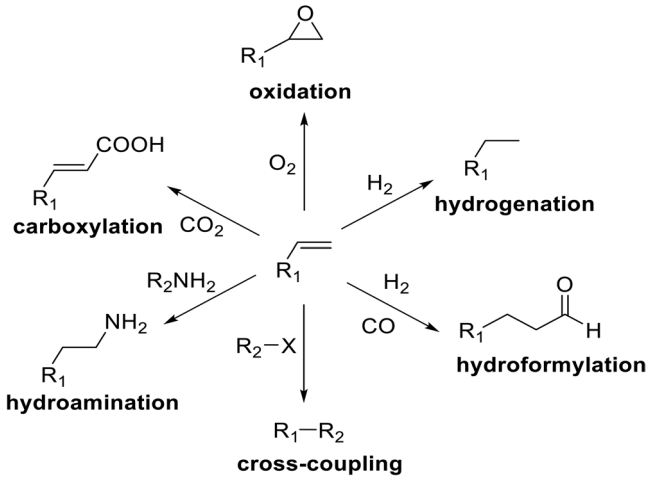
1. Chemoselectivity, when one functional group reacts in the presence of other functional groups present within the same molecule.
2. Regioselectivity, when the reaction takes place at a specific atom in preference to the others within the same functional group.



Scheme 2.2 Reaction selectivity in a chemical transformation.

3. Diastereoselectivity, when the reagent contains a stereogenic centre or diastereotopic faces and can direct the reaction to give two diastereoisomers in a different ratio (d.r., % represents the diastereoisomeric ratio of the possible diastereoisomers).
4. Enantioselectivity, when the substrate is achiral or contains enantiotopic faces and the use of an enantiopure catalyst produces one single enantiomer (e.e., % represents the enantiomeric ratio of the possible enantiomers).

To date, catalysis plays a fundamental role in the production of fuels, polymeric materials and chemical products in industry.[16–29] Even though heterogeneous catalysis is predominantly utilised in industry,[17,30,31] the use of homogeneous catalysts for the synthesis of fine chemicals has increased over the last few decades.[15,32–35] This can be explained by the fact that the mechanism of homogeneous-catalysed processes can be studied in detail easily by using modern techniques to detect reaction intermediates. In particular, great attention has been devoted to the use of metal catalysts to enable a range of chemical transformations such as hydrogenation, hydroformylation or C–heteroatom bond formation reactions (Scheme 2.3).[29,36–41]



Scheme 2.3 Representative transformations of metal-catalysed processes.

2.3 Homogeneous Catalysis

Homogeneous catalysis refers to a catalytic process in which the catalyst and reagents are in the same phase, generally in solution. Even though a great variety of homogeneous catalysts, such as organocatalysts, enzymes, acids and bases or organometallic complexes, have been used for the synthesis of organic molecules and polymers,[42] this book chapter will be strictly focused on the use of metal complexes as homogenous catalysts for chemical transformations.

The most relevant industrial processes catalysed by homogeneous metal catalysts in industry are reflected in Figure 2.1. These processes are usually based on noble metal catalysts that are costly and whose abundance is very limited (Figure 2.2).[43] The choice of the metal centre is crucial to increase the activity and selectivity of a catalytic process, but it is desirable to pursue the use of Earth-abundant metal catalysts to maximise the sustainability of the process, due to their availability and low cost.[44] However, in many cases noble metal-based catalysts display activities and selectivities several orders of magnitude higher than Earth-abundant metal catalysts, such as the Cativa™ process and the Monsanto industrial synthesis of L-DOPA for which an iridium and rhodium catalyst are used, respectively. Iron complexes have shown high catalytic activity and selectivity for a range of organic transformations and are a potential alternative to noble-metal catalysts; however, the catalytic activity displayed by these complexes is usually lower than that observed when ruthenium catalysts are used.[45–47] Therefore, further improvements in the design of sustainable Earth-abundant metal catalysts are required to improve their catalytic activity and selectivity.

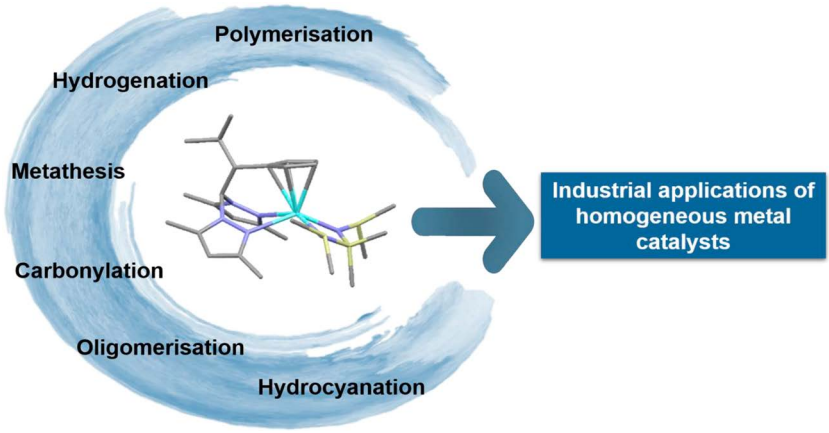


Figure 2.1 Industrial application of homogeneous catalysts to enable chemical transformations.

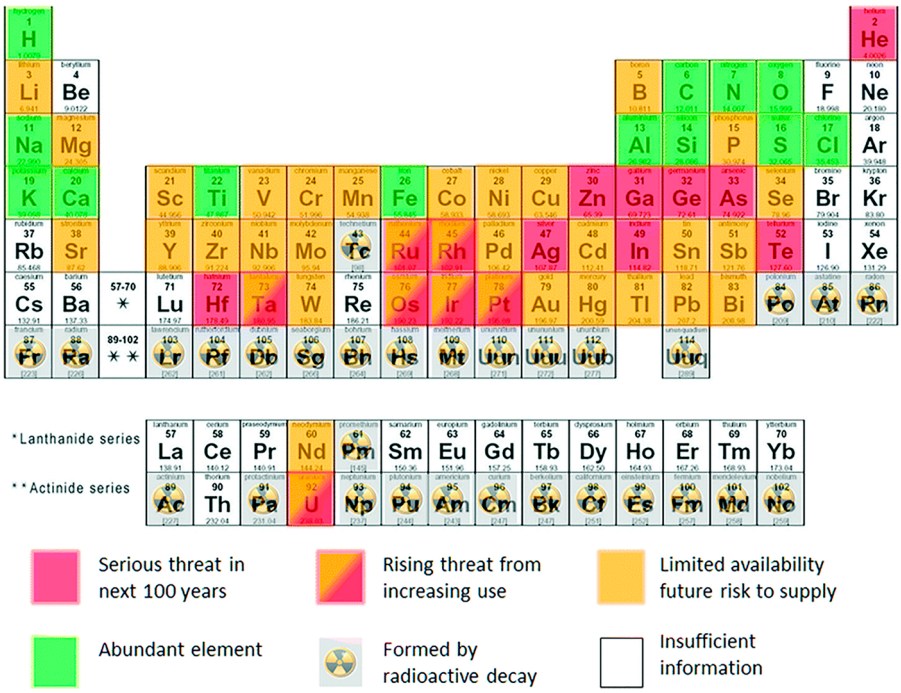
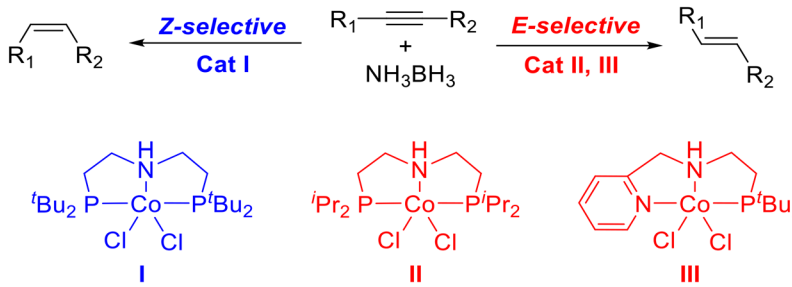
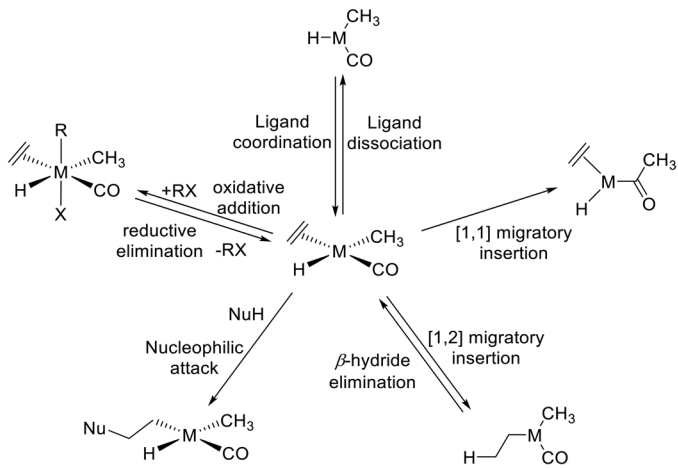


Figure 2.2 Representation of elemental sustainability. Reproduced from ref. 43 with permission from The Royal Society of Chemistry.

Ligand design is also key in homogeneous catalysis. Fine tuning the coordinated ligands may allow the formation of different organic products from the same reagents (see Scheme 2.4).[48] Besides, the catalytic activity can also be modulated for the auxiliary ligands surrounding the metal.[48] In fact, a great variety of metal complexes containing salen, P-based, pincer, porphyrin, scorpionate,



Scheme 2.4 Ligand-controlled hydrogenation of alkynes catalysed by cobalt complexes. Adapted from ref. 48 with permission from The American Chemical Society.



Scheme 2.5 Elementary steps in homogeneous catalysis. Adapted from ref. 42 with permission from Wiley.

and N-heterocyclic carbene ligands, among others, have been reported in the literature.[49–55] The ligand forces the metal centre to adopt a certain geometry and, therefore, improves the activity and selectivity of the catalyst.

Most homogeneous catalytic processes can be described as a combination of elementary reactions, such as ligand coordination and dissociation reactions, oxidative addition and reductive elimination reactions, migratory insertions and β-hydride elimination reactions (Scheme 2.5). Those interested in these elementary steps are recommended to read the following ref. 15 and 42.

2.4 Model Examples

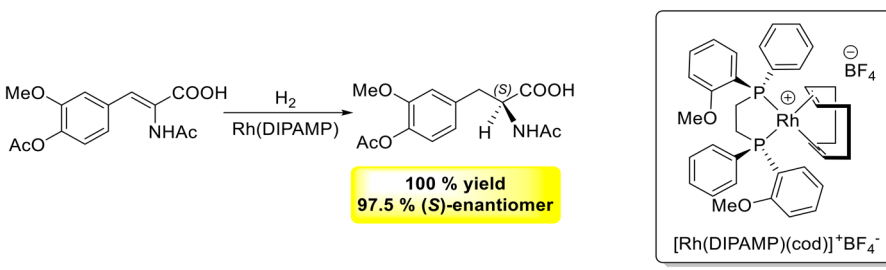
In this section, some remarkable advances in the use of Earth-abundant metal complexes as homogeneous catalysts for hydrogenation processes, C–C and C–heteroatom bond forming reactions and polymerisation reactions for the sustainable synthesis of organic molecules and polymeric materials will be described.

2.4.1 Hydrogenation Reactions

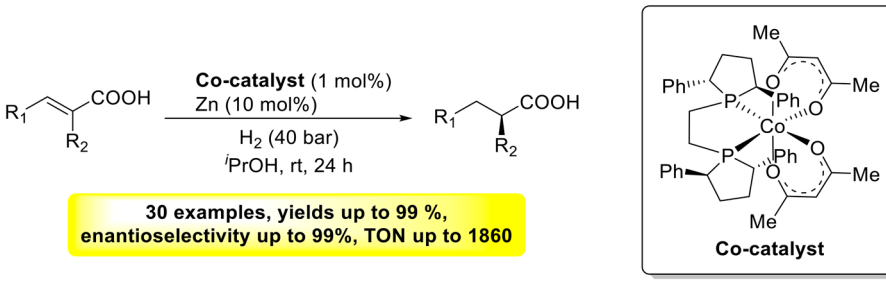
Amongst the different catalytic reactions, the catalytic hydrogenation of unsaturated reagents is the most versatile process. It allows the selective synthesis of a broad range of chemical products in high yield under mild reaction conditions using metal complexes as catalysts. Solid-supported metal catalysts based on Pd, Pt, Rh, Ru and Ni have been used in industry for the chemoselective hydrogenation of organic compounds.[56,57] Since the development of Wilkinson's catalyst,[58] homogeneous catalysts based on Ru, Rh and Ir complexes supported by different enantiopure ligand scaffolds have allowed the stereoselective hydrogenation of unsaturated functional groups (Scheme 2.6).[59,60] In general, the hydrogenation catalyst systems comprise a noble-metal centre and one or more (enantiopure) ligands and anions, which can activate the H_2 molecule and add two hydrogen atoms to the unsaturated group. However, the development of non-precious metal-based complexes as hydrogenation catalysts has risen in recent years due to their lower cost, higher abundance and lower toxicity of the metal centre, in addition to their different reactivity compared to noble-metals.[46,60,61] Nevertheless, the use of precious-metal catalysts is still quite high due to their much higher catalytic activity and productivity, and the high recovery of the catalyst.

Outstanding achievements have been reported on the use of non-noble metal catalysts for hydrogenation processes. A chiral cobalt complex containing an electron-donating diphosphine ligand has been recently developed as a highly effective catalyst for the asymmetric hydrogenation of more than 30 α-substituted α,β-unsaturated acids with enantioselectivities up to >99% e.e. in isopropanol using Zn as an additive (Scheme 2.7).[62] The synthetic protocol has been successfully applied for the enantioselective synthesis of key intermediates in the synthesis of chiral drugs such as (*S*)-Equol, Rupintrivir, Sacubitril, Naproxen, Ibuprofen and Artemisinin. Control experiments and mechanistic studies suggested that the carboxylic acid group may interact with the metal centre to control the catalytic activity and the enantioselectivity of the process, since α,β-unsaturated esters did not react under standard conditions.

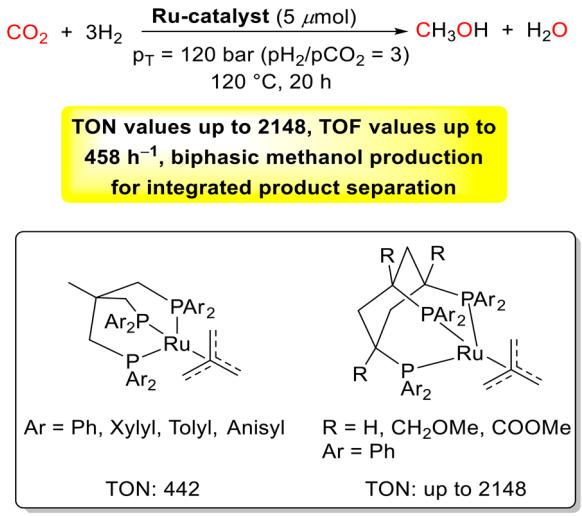
In recent years, many methods for CO_2 hydrogenation have been reported.[63,64] The most promising solution to the global energy problem is the hydrogenation of CO_2 to produce methanol, which is a valuable chemical



Scheme 2.6 Rhodium catalyst for the L-DOPA process.

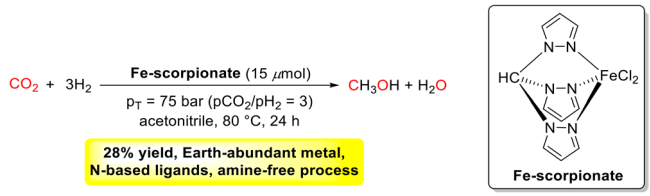


Scheme 2.7 Cobalt-catalysed enantioselective hydrogenation of α,β-unsaturated acids.



Scheme 2.8 Synthesis of methanol using ruthenium complexes containing tripodal P-based ligands.

intermediate for the synthesis of organic molecules and polymeric materials, as a sustainable alternative to the traditional synthesis from CO and H_2. Heterogeneous catalysts have been actively investigated with some success, but the conditions are still too harsh with the requirement of high temperature (>200 °C) and high pressure of CO_2 and H_2 (>50 bar).[63,64] On the other hand, the homogeneous direct hydrogenation of CO_2 to methanol has been less studied than heterogeneous catalysis and has been pursued especially with ruthenium catalysts. The formation of methanol, together with methane and CO, from CO_2 hydrogenation was achieved for the first time by using $Ru_3(CO)_{12}$ as a catalyst in the presence of alkaline iodides under harsh reaction conditions (240 °C, 80 bar).[65] In 2012, ruthenium complexes supported by Triphos ligands were reported as catalysts for the one-pot hydrogenation of CO_2 to methanol (Scheme 2.8).[66] In recent years, a range of tripodal P-based ligands



Scheme 2.9 Synthesis of methanol using an iron scorpionate complex.

have also been synthesised for application in the direct hydrogenation of CO_2, which has resulted in the development of homogeneous catalysts with unprecedented catalytic activity (Scheme 2.8), obtaining TON values up to 1100 for the direct hydrogenation of CO_2 or TON values up to more than 2100 when alcoholic solvents were used.[67–72]

There are only two homogeneous non-noble metal catalytic systems for the direct hydrogenation of CO_2 to methanol. The first Earth abundant metal-based catalyst system reported for this reaction comprised a combination of $Co(acac)_3$, a Triphos ligand and $HNTf_2$ as an acid additive, obtaining TON values up to 78 after 96 hours of reaction in a mixture of solvents THF : EtOH using 20 bar of CO_2 and 70 bar of H_2 pressure at 100 °C.[73]

The use of a scorpionate iron complex is a more sustainable alternative to the use of ruthenium and phosphorous-based ligands for the synthesis of methanol from CO_2 and H_2.[74] This process allows the conversion of carbon dioxide into methanol using an Earth-abundant metal catalyst containing nitrogen-based ligands. The iron compound catalysed the hydrogenation of CO_2 into methanol in acetonitrile using a low catalyst loading at 80 °C and 75 bar of total pressure (pH_2/pCO_2 = 3), obtaining methanol in 28% yield (Scheme 2.9). The use of pentaethylenehexamine (PEHA) was beneficial for the process and allowed an increase in the yield of methanol to 46%. However, even though the yield of methanol is higher when using PEHA, the sustainability of the process increases when the reaction is carried out under amine-free conditions.

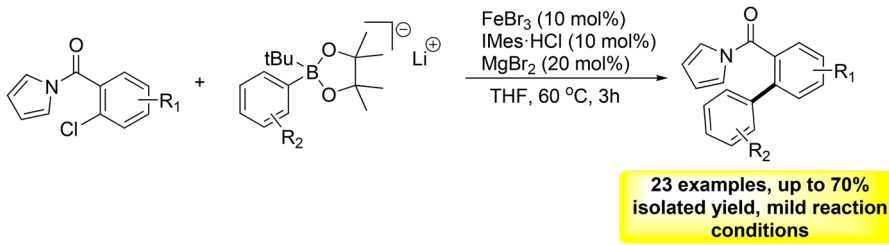
2.4.2 C–C Bond Forming Reactions

Carbon–carbon bond forming reactions are fundamental transformations in organic synthesis. In this context, the development of highly efficient metal complexes as catalysts for C–C bond formation has received much attention.[75–77] Transition metal complexes have been traditionally used to promote C–C bond formation due to their high catalytic activity and functional group tolerance.[75,78–81] However, in recent years there has been a huge expansion in the use of homogeneous iron catalysts as an alternative to noble or expensive transition metal-based catalysts for cross-coupling reactions for the synthesis of pharmaceuticals and natural products.[82–87]

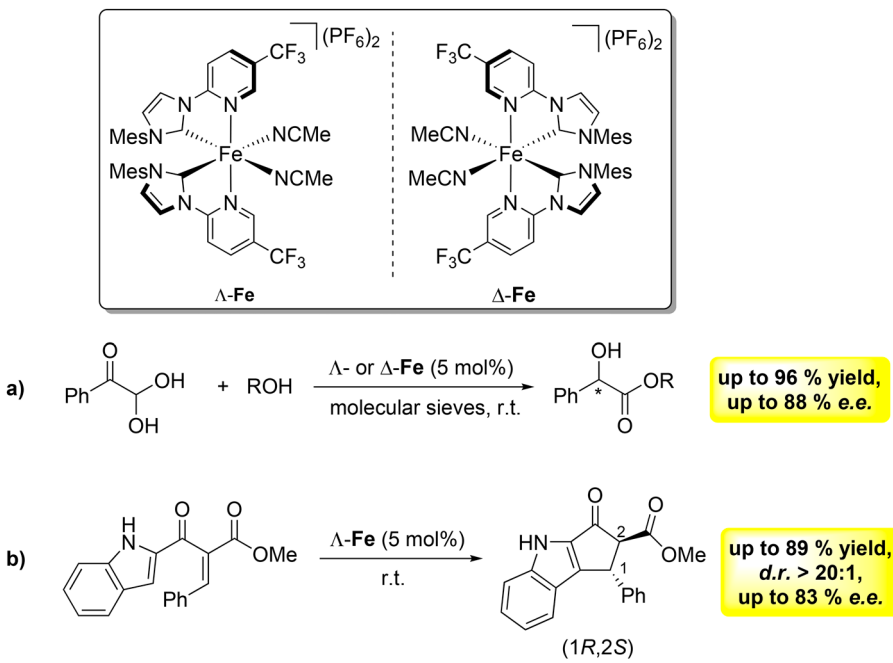
In 2018, the use of an iron(III) complex containing an NHC ligand as a catalyst was reported for the first time for the Suzuki biaryl cross-coupling reaction of organoborates and aryl chlorides at the *ortho* position containing

a π-coordinating directing group such as a pyrrole in the presence of $MgBr_2$ as an additive in THF at 60 °C for 3 hours (Scheme 2.10). Under the optimal reaction conditions, the catalyst system was able to couple a broad range of *N*-pyrrole amide-based aryl chlorides with substituted boronates affording the coupling products from moderate to good yields.[88]

A new class of chiral iron complexes containing two bidentate *N*-(2-pyridyl)-substituted NHC ligands have been recently developed as catalysts for the enantioselective Cannizzaro reaction of phenylglyoxal monohydrate and a broad range of alcohols to afford the corresponding mandelate ester product (Scheme 2.11a).[89] Under the optimised reaction conditions, the chiral-at-iron complexes catalysed the enantioselective formation of the mandelate esters in yields up to 96% and selectivities up to 88%, although



Scheme 2.10 Iron-catalysed Suzuki biaryl cross-coupling reactions.



Scheme 2.11 Chiral iron complexes catalysing the (a) enantioselective Cannizzaro reaction and (b) asymmetric Nazarov reaction.

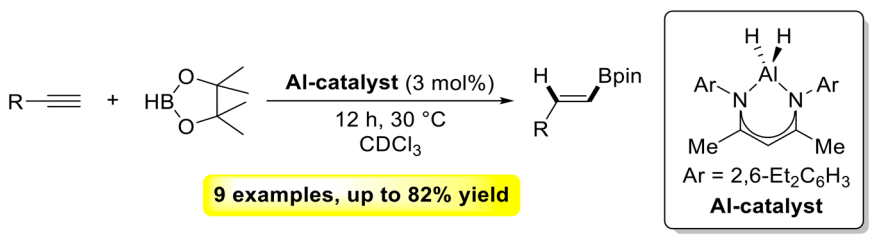
the enantioselectivity is highly dependent on the catalyst loading, the solvent and the alcohol used. This iron complex also catalysed the asymmetric Nazarov cyclisation to afford chiral cyclopentanones in 89% yield, with d.r. > 20:1 and 83% e.e. under the optimal reaction conditions (Scheme 2.11b).[89] The enantiomeric excess was highly dependent on the concentration and the solvent used. This new approach to develop chiral iron complexes containing achiral ligands constitutes a good example to enhance the sustainability of a chemical process, since it combines the use of an Earth-abundant metal centre and easily accessible ligand scaffolds for the development of a highly active and selective catalyst for C–C bond formation.

2.4.3 C–Heteroatom Bond Forming Reactions

The interest in Earth-abundant metal catalysed C–heteroatom bond forming reactions is increasing, since C–heteroatom bonds are present in a broad range of natural products and organic molecules used as building blocks, pharmaceuticals, agrochemicals and smart materials.[90] C–heteroatom bond formation has been traditionally catalysed by precious metal catalysts such as Ir, Rh, Au and Ag,[91–95] but in the last decade much attention has been devoted to the use of Earth-abundant metal-based complexes as catalysts for this transformation.[35,96–100] In this context, aluminium, iron and calcium are the three most abundant metals in the Earth's crust and their complexes have been used with success in a range of C–heteroatom bond formations, such as hydroelementation reactions, N-formylation of amines or the synthesis of cyclic carbonates from epoxides and CO_2.[35,96–100]

A hydride aluminium complex was used as a catalyst for the anti-Markovnikov hydroboration of terminal alkynes with pinacolborane at 30 °C for 12–32 h, obtaining the corresponding *trans*-vinylboronate esters in good to excellent yields (Scheme 2.12).[101] Theoretical investigations concluded that the mechanism proceeds through the formation of an acetylide aluminium complex, which is the rate-determining step.

A calcium scorpionate complex based on highly fluorinated 3-phenyl hydrotris(indazolyl)borate has been shown to be an efficient catalyst for the intramolecular hydroamination reaction of 1-amino-2,2-dimethyl-4-pentene

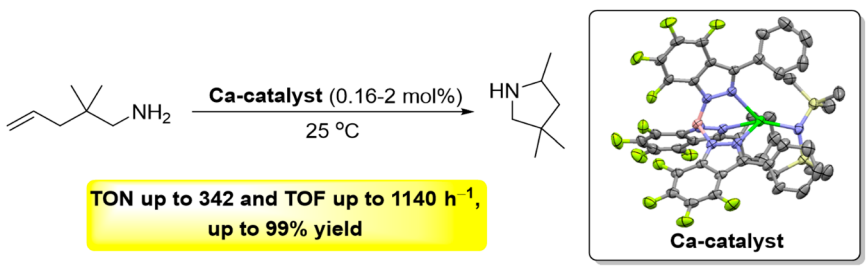


Scheme 2.12 Aluminium-catalysed anti-Markovnikov hydroboration of terminal alkynes.

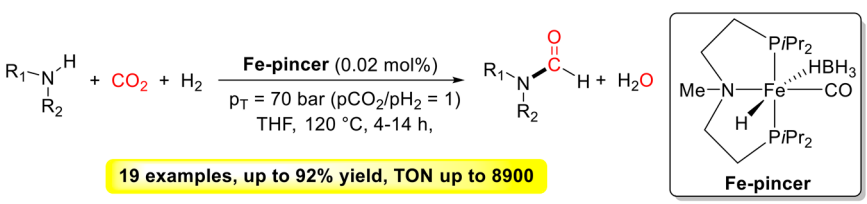
at room temperature, obtaining the corresponding cyclic amine in good to excellent yields (57–99%) after only 6–27 minutes depending on the [substrate]:[Ca] ratio (Scheme 2.13).[102] The hydroamination reactions are first order with respect to the concentration of the substrate and the concentration of the catalyst. It is worth highlighting that this Ca complex constitutes one of the most active catalysts for the cyclohydroamination of 1-amino-2,2-dimethyl-4-pentene, obtaining TON and TOF values up to 342 and 19 min^{-1}, respectively.

A well-defined pincer iron complex has been recently developed as a highly efficient catalyst for the N-formylation of a broad range of amines through the hydrogenation of CO_2, obtaining the corresponding amide products in moderate to excellent yields using 0.02 mol% of catalyst loading (Scheme 2.14).[103] This pincer iron complex represents one of the most active catalysts for the N-formylation of amines, obtaining TON values higher than 4500 and high conversions after 4 hours.

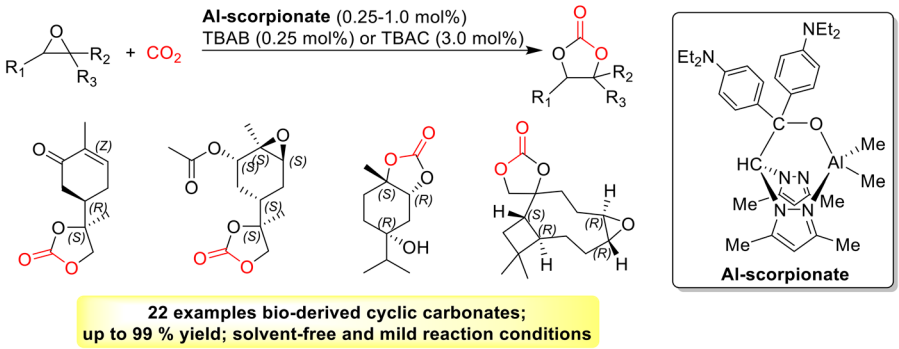
Cyclic carbonate formation from epoxides and CO_2 is a 100% atom economic process that has been catalysed by a broad range of aluminium complexes.[43] In this context, bimetallic salen aluminium complexes have been shown to be excellent catalysts for this process even at room temperature and pressure, using tetrabutylammonium bromide (TBAB) as a cocatalyst.[104–110] Aminotriphenolate aluminium catalysts have also been developed as highly efficient catalysts for cyclic carbonate formation,[111–113] obtaining TOF values up to 906 h^{-1}. These complexes were shown to also be active for the synthesis of terpene-derived cyclic carbonates with high diastereoselectivity.[114]



Scheme 2.13 Calcium-catalysed hydroamination of aminoalkenes.



Scheme 2.14 Iron-catalysed N-formylation of amines *via* hydrogenation of CO_2.



Scheme 2.15 Aluminium-catalysed synthesis of bioderived cyclic carbonates.

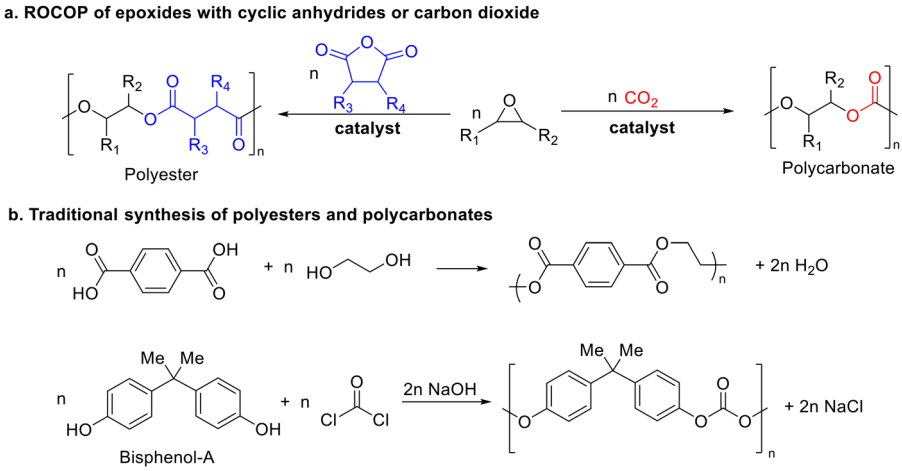
Scorpionate aluminium complexes have displayed good catalytic activity for the reaction of carbon dioxide and epoxides to afford a broad range of cyclic carbonates.[115–121] Amongst them, a scorpionate aluminium complex has recently been developed as a catalyst for the synthesis of a broad range of furan-, diacid- and terpene-derived cyclic carbonates from their corresponding bio-based epoxides and CO_2 under mild and solvent-free reaction conditions (Scheme 2.15).[122] It is worth highlighting that the synthesis of terpene-derived cyclic carbonates occurred with excellent diastereoselectivity, obtaining one single diastereoisomer in some cases. Moreover, some of the bis(cyclic carbonates) synthesised were used as bio-derived building blocks for the synthesis of non-isocyanate polyurethane materials *via* ring-opening reactions with 1,4-diaminobutane and 1,3-bis(aminomethyl)cyclohexane.

2.4.4 Polymerisation Reactions

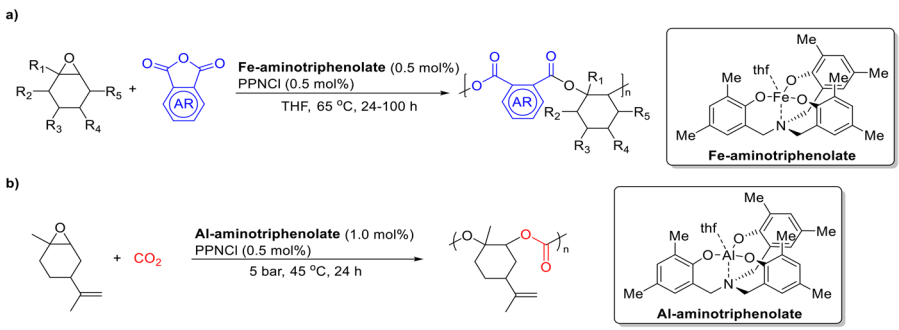
The development of sustainable biodegradable polymeric materials to replace current petroleum-derived plastics is one of the biggest challenges for researchers in academia and industry. In this context, the use of appropriate metal-based catalysts for the catalytic transformation of renewable feedstocks into sustainable polymers is essential to accomplish such a challenge. The most relevant achievement in homogeneous catalysis by the use of Earth-abundant metals corresponds to the preparation of polyester and polycarbonate materials derived from bio-derived feedstocks *via* ring-opening copolymerisation (ROCOP) processes (Scheme 2.16a) as an alternative to the traditional synthesis of polyester and polycarbonate materials (Scheme 2.16b).

Homogeneous catalyst systems based on Al(III), Co(III), Cr(III), Fe(III) and Zn(II) supported by a broad range of ligands have been developed in recent decades and have displayed excellent catalytic activity and selectivity towards the ROCOP of (bioderived) epoxides and cyclic anhydrides or carbon dioxide to afford either polyester or polycarbonate materials (Scheme 2.17).[123–128]

The combination of an aminotriphenolate iron complex and PPNCl afforded the preparation of a broad range of bioderived polyesters from terpene oxides and aromatic anhydrides (Scheme 2.17a).[129] The polymerisation



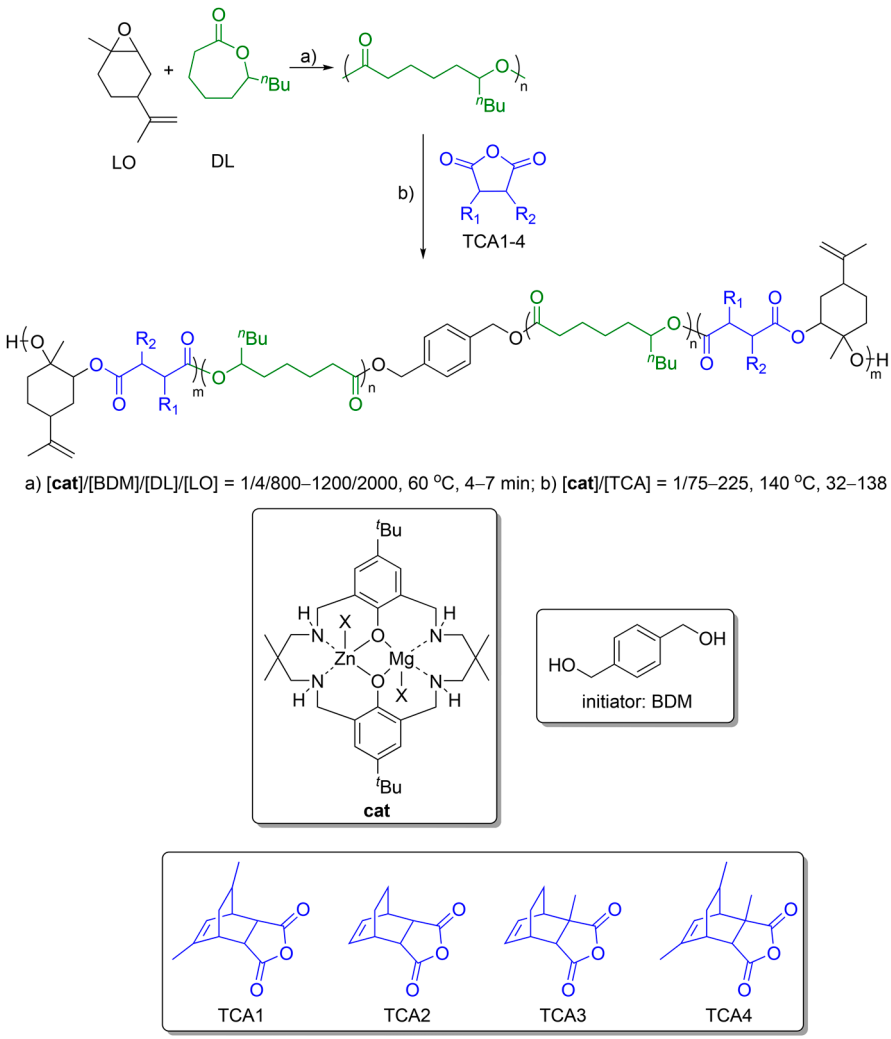
Scheme 2.16 (a) Ring-opening copolymerisation processes for the synthesis of polyesters or polycarbonates. (b) Traditional synthesis of polyesters and polycarbonates.



Scheme 2.17 (a) Iron-catalysed ROCOP of bioderived epoxides and aromatic cyclic anhydrides. (b) Aluminium-catalysed ROCOP of limonene oxide and carbon dioxide.

processes were carried out under mild reaction conditions using 0.5 mol% of catalyst loading in THF at 65 °C, obtaining the corresponding medium to high molecular weight polyester materials with a selectivity higher than 98%. It is worth highlighting that the thermal properties of the polyester materials prepared were highly dependent on the structure of the starting materials, obtaining glass transition temperatures (T_g) ranging from 53 to 243 °C. The same research group also employed an aminotriphenolate aluminium complex as the catalyst for the reaction of limonene oxide with carbon dioxide for the synthesis of stereoregular medium to high molecular weight polycarbonates with narrow polydispersities derived from renewable resources under mild and solvent-free reaction conditions (Scheme 2.17b). Although the catalyst system was able to convert both *cis*- and *trans*-LO, it showed preference for the ROCOP of carbon dioxide with *cis*-LO over *trans*-LO, obtaining the corresponding polycarbonate with around 70% *trans* units in its structure.[130]

The use of potentially renewable and fully renewable monomers for the synthesis of new bioderived and degradable block polyesters with high renewable content *via* ROCOP of limonene oxide (LO), ε-decalactone (DL) and tricyclic anhydrides (TCA) has been recently reported using a hetero-bimetallic complex as a catalyst in the presence of 1,4-benzene dimethanol as an initiating system at 140 °C (Scheme 2.18).[131] These block copolyester materials were investigated as pressure-sensitive adhesives, showing that for



Scheme 2.18 Synthesis of bioderived block copolyesters *via* ROCOP of limonene oxide, ε-decalactone and tricyclic anhydrides catalysed by a hetero-bimetallic complex.

the same tricyclic anhydride, the peel adhesion increased when increasing the polyester content obtained *via* ROCOP of LO and TCA. Their mechanical and rheological properties are similar to commercial materials and constitute good examples of sustainable biodegradable polymeric materials to replace current commercial materials.

2.5 Conclusions

The use of Earth-abundant metal-based complexes as catalysts for a wide range of chemical transformations, such as hydrogenation, C–C and C–heteroatom bond formation and polymerisation reactions, is a sustainable alternative to the use of noble and precious metals. However, catalyst development is still required in order to match the catalytic activity obtained with precious-metal catalysts. Some outstanding results have been achieved using aluminium and iron catalysts amongst other Earth-abundant transition metal catalysts. These processes often occur *via* a different mechanism than when using noble-metal catalysts and have shown broad substrate scope and high catalytic activity under mild reaction conditions, obtaining the final products with excellent yields and/or selectivities. Despite the excellent results that Earth-abundant metal catalysts have shown, there are not many large-scale industrial applications for them. An alternative to increase the sustainability of the processes and implement them in industrial processes could be the development of supported homogeneous catalysts onto polymers or silica. This would improve catalyst separation and reusability.

On the other hand, the use of unsustainable solvents or reagents recently added to the "REACH" restricted chemical list should be avoided in order to develop greener chemical processes.[132] Further research is essential to (i) develop more active and selective homogeneous Earth-abundant metal catalysts, (ii) fully understand the mechanism of chemical processes catalysed by abundant-metal complexes, and (iii) translate the academic research into sustainable industrial processes.

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