Chapter 2
Atom Economy and Reaction Mass Efficiency

Abstract The green metrics atom economy (AE) and reaction mass efficiency (RME) are introduced and discussed. Following literature definitions, examples of reactions appropriate for upper-level undergraduate students are provided to illustrate how the metrics are calculated. In the case of atom economy, important assumptions regarding reactants, solvents and reagents are identified and explained. Several examples of inherently atom-efficient and inefficient reactions are also provided. In terms of reaction mass efficiency, the focus centers on a concise mathematical breakdown of various factors which contribute to changes in RME values in the context of two well-established definitions. A view of RME as a more robust metric that better captures the materials used during a chemical transformation is developed in the context of an undergraduate Suzuki reaction. With numerous academic and industrial examples comparing traditional syntheses with modern catalytic routes, the benefits and limitations of AE and RME are considered. Along with real-world case studies, the useful and effective application of these metrics is explained using several definitions of an ideal chemical reaction as points of reference. Finally, future projections and academic work are briefly outlined in order to highlight the development of these important metrics.

Keywords Atom economy · Reaction mass efficiency · Generalized reaction mass efficiency · Suzuki reaction · Product yield · Heterogeneous catalysis · Homogeneous catalysis · Biocatalysis

2.1 Atom Economy

2.1.1 Development and Motivation

The concept of atom economy (AE) was introduced in 1991 by Barry M. Trost at Stanford University [1]. In the past, the material efficiency of a chemical reaction was routinely quantified by measurement of the product yield, with an ideal value

of 100 %. Atom economy has since sparked a "green" paradigm shift, as chemists began viewing reactions in terms of *how much* of the reactants are converted into a desired product. With the goal of achieving "synthetic efficiency in transforming readily available starting materials to the final target" [1], the primary motivation was to maximize the incorporation of reactant atoms into final products. This goal has led many chemists to focus their attention on adopting and developing processes that were inherently atom-efficient (Sect. 2.1.3). To help achieve higher selectivity and efficiency in organic syntheses, the application and development of catalytic systems was emphasized (Sect. 2.1.4). The development of theoretical aspects of atom economy has occurred both in isolation [2–5] and from the point of view of green metrics [6–8]. Collectively, these works illustrate the power of green metrics, their virtues and limitations, and their ability to promote innovation and change with regard to sustainable practice.

2.1.2 Definition and Key Assumptions

The ideal atom economy for a chemical transformation is taken as the process where all reactant atoms are found in the desired product [1]. In other words, atom economy is a calculation which measures "how much of the reactants remain in the final product" [6]. The percent atom economy of a generic stoichiometric chemical reaction to synthesize compound C is shown in Fig. 2.1. Since the calculation is essentially the molecular weight ratio of the final product divided by the sum of all reactants, it is possible to determine the atom economy for a reaction prior to undertaking any experimental work.

This calculation extends to a multi-step process where intermediates that are formed in one step and consumed during a later step are neglected (Fig. 2.2). Certain key assumptions about reactants, catalysts and reaction stoichiometry are necessary when calculating atom economy [6]. Firstly, a reactant is understood as any material that is incorporated into an intermediate or product during the synthesis. This includes protecting groups, catalysts used in stoichiometric quantities and acids or bases used for hydrolysis. Solvents, reagents or materials used in catalytic quantities are omitted from the analysis, as they do not contribute atoms to an intermediate and/or product.
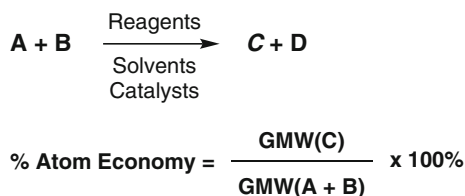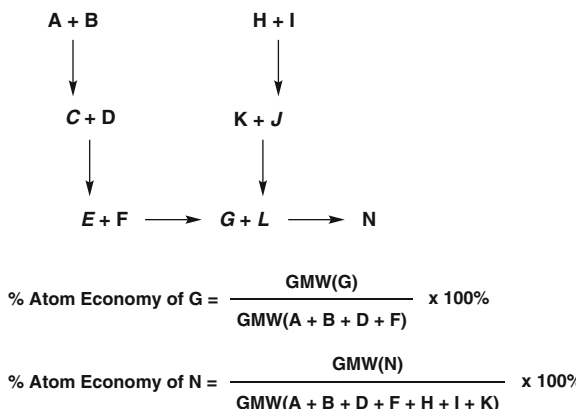
$$\text{A + B} \xrightarrow[\substack{\text{Solvents} \\ \text{Catalysts}}]{\text{Reagents}} \text{C + D}$$

$$\% \text{ Atom Economy} = \frac{\text{GMW(C)}}{\text{GMW(A + B)}} \times 100\%$$

Fig. 2.1 Atom economy calculation for the synthesis of C

Fig. 2.2 Atom economy
calculations for products
G and N

$$\text{\% Atom Economy of G} = \frac{\text{GMW(G)}}{\text{GMW(A + B + D + F)}} \times 100\%$$

$$\text{\% Atom Economy of N} = \frac{\text{GMW(N)}}{\text{GMW(A + B + D + F + H + I + K)}} \times 100\%$$

A second assumption states that the chemical equation (which includes all starting materials and products) has been fully and correctly balanced. For example, if three equivalents of an inorganic base are consumed during a transformation such as the Suzuki reaction, three base equivalents must be included in the calculation of atom economy (Scheme 2.1) [9]. It is useful to think of atom economy in terms of accounting for consumed reactant material. Note that the calculation does not reflect actual experimental masses and volumes. Moreover, knowledge of reaction mechanisms is highly recommended. Many of these elements are discussed in greater detail elsewhere [5–7].

$$\text{\% Atom Economy} = \frac{170.21}{121.93 + 220.01 + 3 \times 138.20} \times 100\% = 22.5\%$$
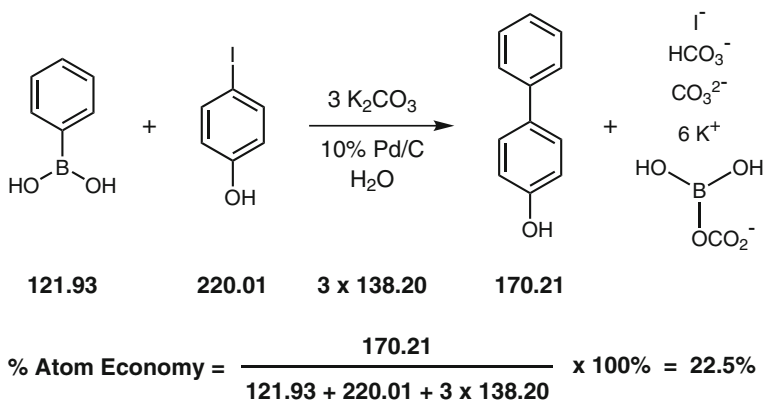
Scheme 2.1 Atom economy of a balanced Suzuki reaction

## *2.1.3 Reaction Types: The Good, the Bad and the Ugly*

Atom economy calculations generally show that addition and rearrangement reactions are preferred over substitutions and eliminations. The mercury (II)-catalyzed hydration of alkynes and the benzilic acid rearrangement are examples of 100 % atom-efficient reactions (Scheme 2.2) [10].

Although rearrangements often proceed with perfect atom economy, certain addition reactions do not. Examples include an osmium tetroxide-mediated dihydroxylation and a Simmons-Smith cyclopropanation reaction (Scheme 2.3) [11]. In particular, the mechanism of the Simmons-Smith reaction shows that a significant portion of the starting materials ends up as molecular waste [12]. This inefficiency provides opportunities for designing new reactions with the goal of improving atom economy.

For example, the Upjohn dihydroxylation uses *N*-methylmorpholine *N*-oxide (NMO) as a cheap co-oxidant to render the toxic and expensive osmium tetroxide catalytic via re-oxidation (Scheme 2.4) [11, 13]. In a recent article, Maurya et al. described a new catalyst-free cyclopropanation which uses electron-deficient alkenes (Scheme 2.5) [14]. In this reaction, the increased electrophilicity of doubly-activated alkenes facilitates a Michael-induced ring closure with ethyl diazoacetate. By eliminating stoichiometric reagents and minimizing waste, a much higher atom economy is achieved. Addition reactions are therefore excellent candidates for designing more atom-efficient processes [3–5, 8, 15].

Although substitution and elimination reactions are intrinsically wasteful (Scheme 2.6), there exists opportunities to design for better atom economy. For
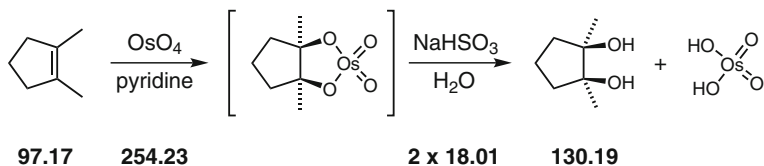

Scheme 2.2 Atom economy calculations for the Hg^{2+}-catalyzed hydration of an alkyne and a benzilic acid rearrangement
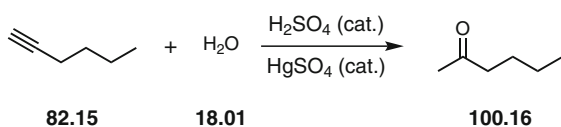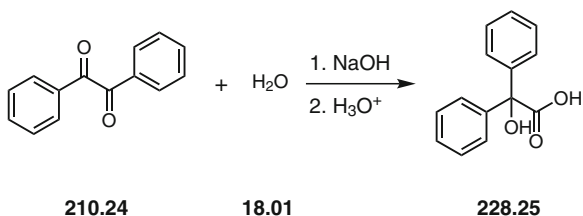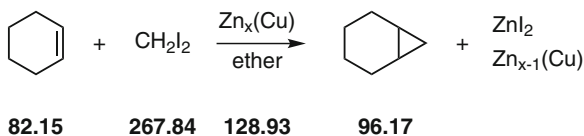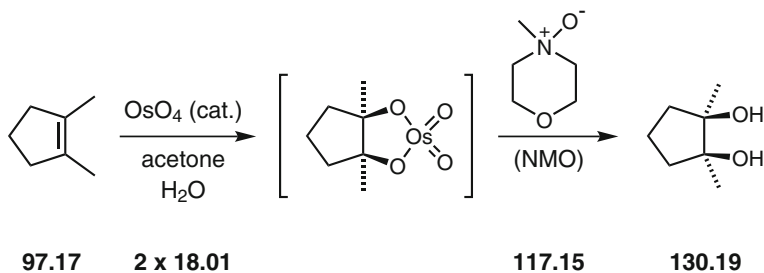
$$\% \text{ Atom Economy} = \frac{130.19}{97.17 + 254.23 + 2 \times 18.01} \times 100\% = 34\%$$

$$\% \text{ Atom Economy} = \frac{96.17}{82.15 + 267.84 + 128.93} \times 100\% = 20\%$$

Scheme 2.3   Atom economy calculations for an osmium tetroxide-mediated dihydroxylation and a Simmons-Smith cyclopropanation
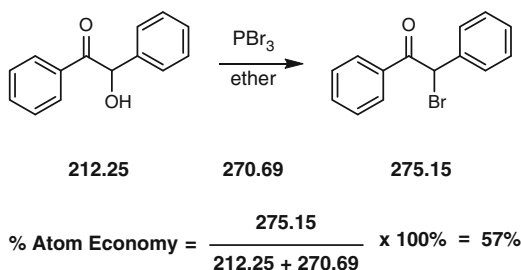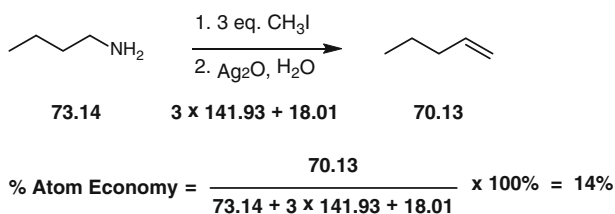

$$\% \text{ Atom Economy} = \frac{130.19}{97.17 + 2 \times 18.01 + 117.15} \times 100\% = 52\%$$

Scheme 2.4   Improved atom economy of an OsO$_4$-mediated dihydroxylation using N-methyl-morpholine as a co-oxidant

example, the preparation of alkyl halides from alcohols is routinely effected with either phosphorus tribromide (PBr$_3$, Scheme 2.6) or thionyl chloride (SOCl$_2$, Scheme 2.7) [16]. Choosing the appropriate substitution involves deciding between gaining access to a better leaving group (Br) for further reaction, or including a step with a higher atom economy. Recent work in substitution reactions has shown that catalytic conditions can also improve atom economy [17, 18].

$$\% \text{ Atom Economy } = \frac{319.16}{233.07 + 114.10} \times 100\% = 92\%$$
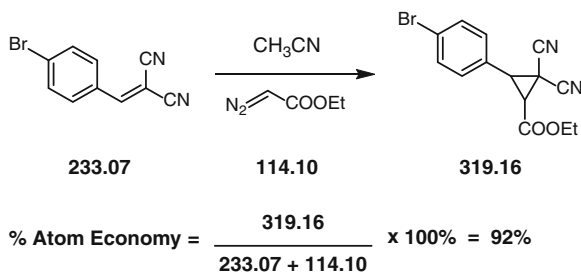
Scheme 2.5 Atom-economic catalyst-free cyclopropanation of an electron deficient alkene with ethyl diazoacetate

$$\% \text{ Atom Economy } = \frac{70.13}{73.14 + 3 \times 141.93 + 18.01} \times 100\% = 14\%$$

$$\% \text{ Atom Economy } = \frac{275.15}{212.25 + 270.69} \times 100\% = 57\%$$

Scheme 2.6 Atom economy calculations for a Hofmann elimination and bromination of a secondary alcohol with PBr$_3$

Scheme 2.7 Atom economy calculation for chlorination of a secondary alcohol with SOCl$_2$

$$\% \text{ Atom Economy } = \frac{230.69}{212.25 + 118.96} \times 100\% = 70\%$$
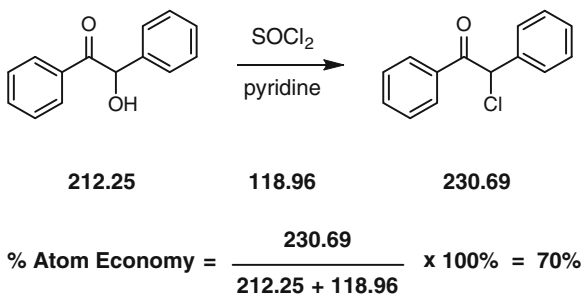
2.1.4 Catalysis, Industry and Innovation

Reaction catalysis is generally understood in terms of kinetics, with an emphasis on the enhanced rate of a chemical process in the presence of a regenerated catalyst. Because they are not consumed, catalysts are omitted from the formal calculation of atom economy. Catalysts work by providing an alternative reaction pathway involving lower energy transition states and a lower activation barrier for the reaction rate-determining step [19]. Catalysis can therefore promote atom-efficient reactions which are otherwise energetically disfavoured. With the use of heterogeneous, homogeneous and biocatalytic strategies, it is possible to reduce (if not eliminate) experimental constraints such as extra synthetic steps, stoichiometric components and energy inputs. Consequently, it is possible to undertake not just greener syntheses, but ones with higher atom economies.

2.1.4.1 Heterogeneous Catalysis

A process where a catalyst in one phase (usually a solid) interacts with reactants in a different phase (usually a gas or liquid) is called *heterogeneous catalysis*. This interaction occurs via adsorption of reactants onto the surface of the catalyst. A fuller discussion of the principles of heterogeneous catalysis has been published elsewhere [19, 20]. In many sources, examples of applied heterogeneous catalysis on an industrial scale frequently cite the preparation of ethylene oxide [21, 22] and the nickel-catalyzed hydrogenation of nitrobenzene [22, 23] (Scheme 2.8). In the case of nitrobenzene, the original process had an atom economy of 35 %. When combined with the loss of valuable iron-containing reactants, it was clear that a cheaper more efficient process was necessary to accommodate the global demand for aniline. To help solve this problem, nickel was picked as a cheap, robust and easily recyclable heterogeneous catalyst for the production of aniline. The new nickel-catalyzed process thus achieved an atom economy of 72 %. The synthesis of aniline has also proven valuable from a pedagogical perspective. In a recent article, Mercer et al. have described a student-driven multi-metric analysis of five different routes towards the production of aniline from benzene [24].

In 2007, the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (ACS GCI PR) created a research agenda to promote areas of mutual interest for advancing green chemistry principles [25]. One area requiring significant improvement was amide bond formation, with a special emphasis on the need to eliminate inefficient reagents such as carbodiimides, and phosphonium/uranium salts, among many others. The inefficiency of many amide bond coupling reagents, their tendency to form toxic or corrosive by-products, and their costly waste streams have been discussed in the literature [26]. Since the Roundtable's findings, numerous solutions to this problem have been proposed [27]. A promising approach emerged in 2009 [28] featuring the use of thermally-activated K60 silica as an affordable, readily available and benign heterogeneous catalyst (Scheme 2.9).
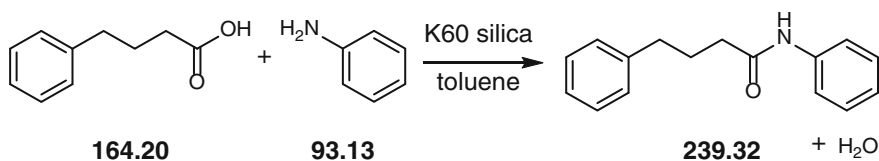
Traditional Béchamp Process:
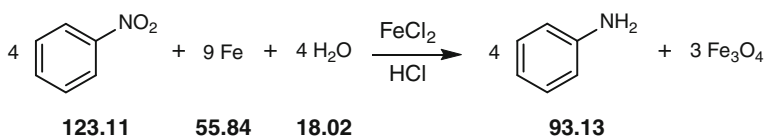
$$\% \text{ Atom Economy } = \frac{4 \times 93.13}{4 \times 123.11 + 9 \times 55.84 + 4 \times 18.02} \times 100\% = 35\%$$

Nickel Catalyzed Hydrogenation Process:
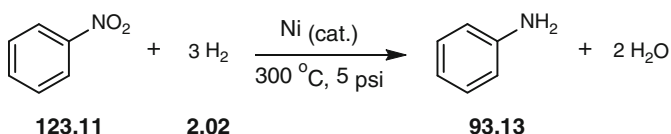
$$\% \text{ Atom Economy } = \frac{93.13}{123.11 + 3 \times 2.02} \times 100\% = 72\%$$
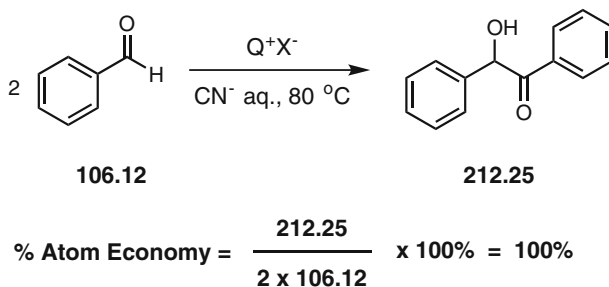
Scheme 2.8 Atom economy calculations for the traditional Béchamp process and the nickel-catalyzed hydrogenation of nitrobenzene


$$\% \text{ Atom Economy } = \frac{239.32}{164.20 + 93.13} \times 100\% = 93\%$$

Scheme 2.9 Atom economy calculation for the K60 silica catalyzed synthesis of 4, *N*-diphenylacetamide

   Although high temperatures were required to prevent the product from becoming trapped within silica pores, the reaction between 4-phenylbutanoic acid and aniline produced a yield of 74 % with an atom economy of 93 %. Furthermore, the authors carried out continuous flow experiments to demonstrate both catalyst recyclability and reaction completion on scales required for industrial applications. On a different note, an important subclass of heterogeneous catalysis is phase-transfer catalysis. Phase-transfer catalysts work to adsorb reactants and transfer them between liquid phases to promote reactivity. Recent work outlined use of quaternary ammonium salts as benign reusable pseudo-phase-transfer catalysts for a benzoin condensation carried out in water, which occurs with 100 % atom economy (Scheme 2.10) [29].

% Atom Economy = $\dfrac{212.25}{2 \times 106.12}$ x 100% = 100%

Scheme 2.10 Atom economy calculation for a benzoin condensation catalyzed by a quaternary ammonium salt (Q^+X^-)

% Atom Economy = $\dfrac{86.18}{2 \times 58.12}$ x 100% = 74%
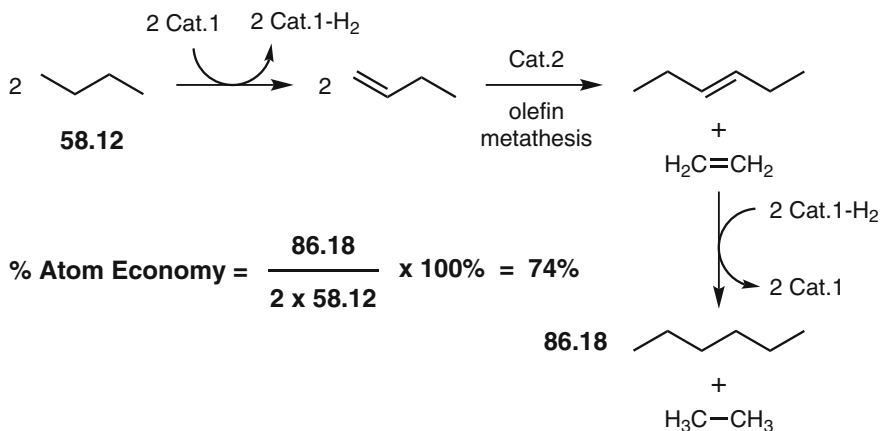
Scheme 2.11 Atom economy calculation for the metathesis of butane using a dual-catalyst system

Another approach in applying heterogeneous catalysis involves combining multiple catalysts in a single system. In 2006, Goldman et al. used two catalysts to carry out the metathesis of *n*-alkanes (Scheme 2.11) [30]. A "pincer"-ligated iridium complex was used as the hydrogen transfer catalyst to effect both alkane dehydrogenation and olefin hydrogenation. A standard solid phase catalyst was used for olefin metathesis. The high atom economy and selectivity achieved by this system makes the approach very elegant. Current research in heterogeneous catalysis is aimed at designing recyclable high-selectivity catalysts for reactions requiring C–H activation [31].

2.1.4.2 Homogeneous Catalysis

Homogeneous catalysis takes place in a system where reactants and catalysts are found in the same phase (usually both liquids). As distinguished from a heterogeneous

process which involves surface chemistry, homogeneous catalysis proceeds via discrete association and dissociation steps within solution. For simplicity one can separate homogeneous catalysis into two categories: those involving metal complexes, and others without metals. The former is often referred to as organometallic catalysis while the latter involves acid/base catalysis and organocatalysis. For more details on this topic the reader is referred to an excellent book written by Rothenberg [19].

Although heterogeneous catalysis is applied in nearly 90 % of industrial processes, homogeneous catalysis is gaining momentum [19]. The 1970 du Pont adiponitrile synthesis catalyzed by a nickel-tetrakis(phosphite) complex is an example of a major industrial process occurring with 100 % atom economy (Scheme 2.12) [32, 33]. Moreover, in terms of advancing green chemistry principles, an article by Allen and Crabtree effectively demonstrates ways to improve upon catalytic systems that are already deemed green [34]. Along the same lines, the traditional approach to β-alkylation of alcohols consists of a three-step atom inefficient route (Scheme 2.13). Earlier work by Crabtree's group had identified

$$\% \text{ Atom Economy} = \frac{108.14}{54.09 + 2 \times 27.03} \times 100\% = 100\%$$
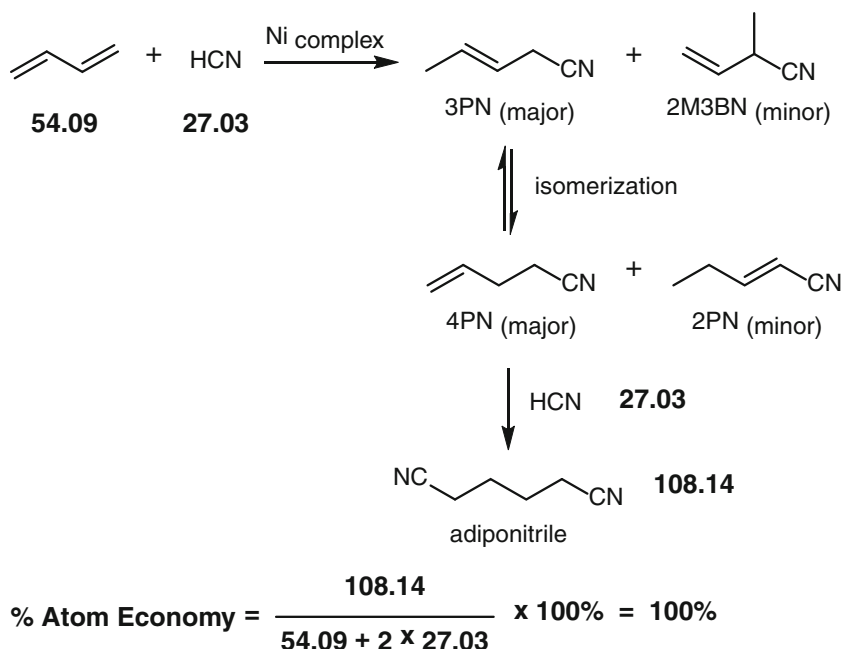
Scheme 2.12 Atom economy calculation for the nickel-catalyzed synthesis of adiponitrile
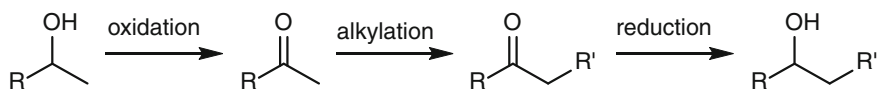

**Scheme 2.13** Traditional three-step β-alkylation of alcohols

homogeneous iridium and ruthenium catalyst complexes giving a one-pot β-alkylation with an atom economy of 62 % [35, 36].

In a recent article, Crabtree et al. used an alkali metal base to catalyze the same β-alkylation (Scheme 2.14) [34]. The proposed mechanism starts with an Oppenauer oxidation in air, followed by a base-catalyzed aldol reaction, and ending with a Meerwein–Ponndorf–Verley-type reduction [37]. Aside from an improved atom economy, the method demonstrated a lower energy input and use of cheaper, less toxic earth metals as opposed to transition metals.

Finally, an important technique gaining traction in homogeneous catalysis is the idea of "hydrogen borrowing". This approach uses catalysts as carriers of hydrogen atoms to promote redox-neutral reactions such as an alcohol-amine coupling (Scheme 2.15). Following this strategy, researchers made a GlyT1 inhibitor for the treatment of schizophrenia on a kilogram scale using an iridium complex as the catalyst [38]. Although many catalytic systems break down when involved in scale-up,

$$\% \text{ Atom Economy} = \frac{212.29}{122.17 + 108.14 + 56.11} \times 100\% = 74\%$$
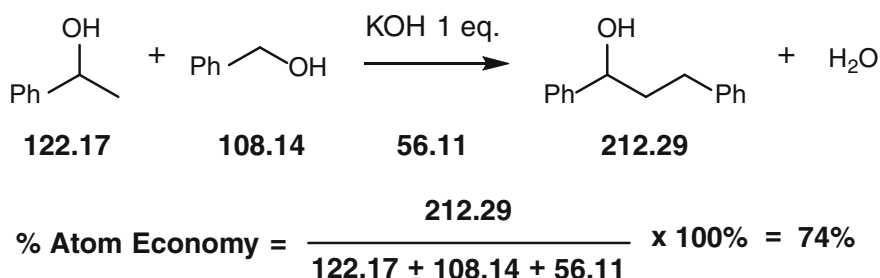
Scheme 2.14 Atom economy calculation for base-catalyzed β-alkylation of a secondary alcohol
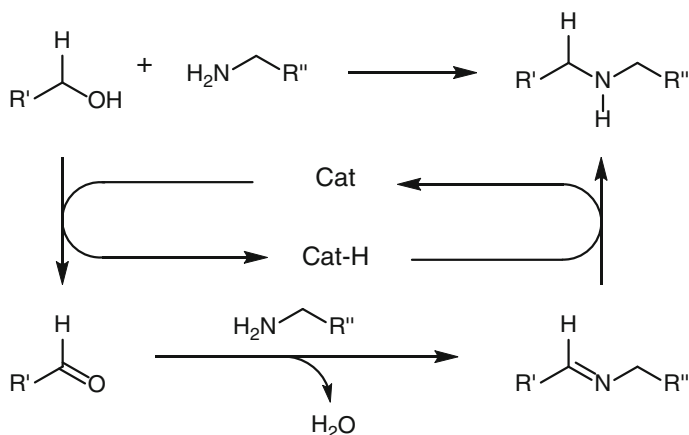
Scheme 2.15 Redox-neutral alcohol-amine coupling using hydrogen borrowing. Adapted with permission from [38]. Copyright 2011 American Chemical Society

this atom-efficient process working at near industrial scale demonstrates the versatility afforded by homogeneous catalysis.

2.1.4.3 Biocatalysis

Biocatalysis requires using enzymes to promote chemical reactions. Although enzymes have numerous green chemistry advantages including biodegradability, safety and high selectivity, it has been estimated that only about 130 routes have been commercialized as of 2002 [39]. This figure has steadily risen due to advances in recombinant DNA technology, protein engineering and immobilization methods that make the production, manipulation and optimization of enzymes economically feasible [40, 41].

   In terms of atom economy, the manufacture of 6-aminopenicillanic acid (6-APA) from penicillin G highlights the power of biocatalysis. 6-APA is an important precursor to penicillin and cephalosporin antibiotics and has been traditionally made by a four-step deacylation process (Scheme 2.16) [42].

   The route involved silyl protection of the penicillin G carboxyl group, transformation of the secondary amide moiety into an imine chloride with phosphorous pentachloride, enol ether formation, and finally hydrolysis leading to an overall atom economy of 28 %. In a 2001 review, Sheldon et al. explained the development of the biocatalytic process which uses a stable penicillin G acylase enzyme having an atom economy of 58 % (Scheme 2.17) [43]. Owing to a dramatic reduction in

$$\% \text{ Atom Economy} = \frac{216.26}{372.48 + 108.64 + 208.22 + 74.12} \times 100\% = 28\%$$
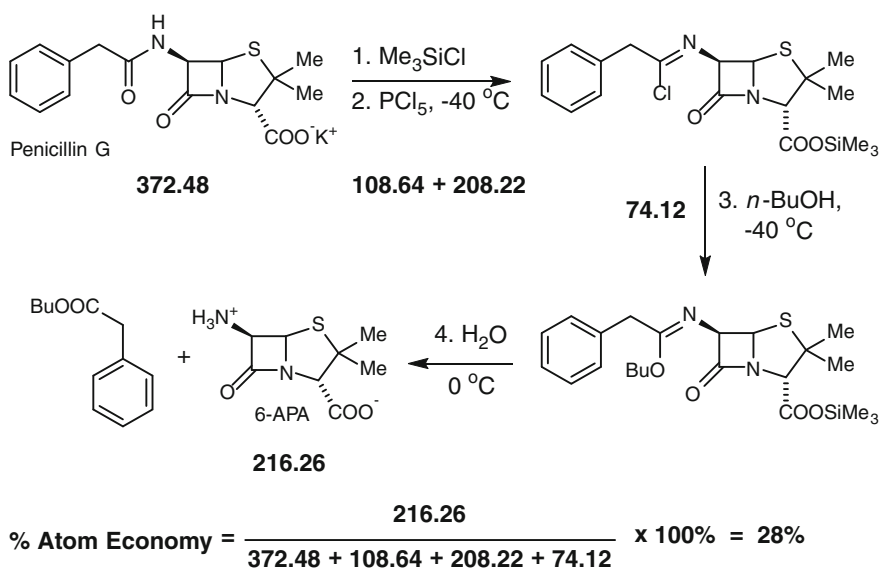
Scheme 2.16 Atom economy calculation for the traditional 4-step deacylation of penicillin G to 6-aminopenicillanic acid (6-APA)
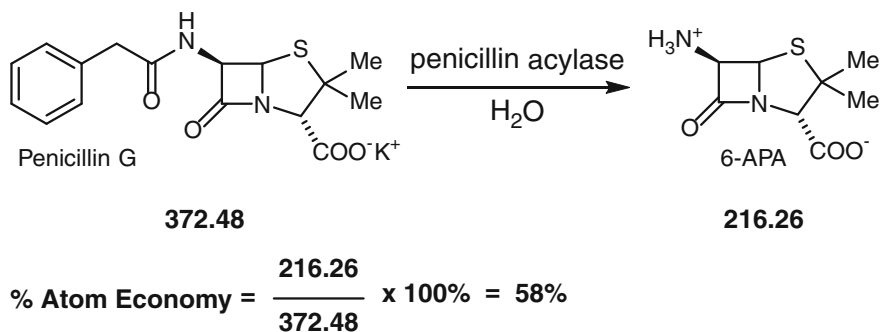
Scheme 2.17 Atom economy calculation for the penicillin acylase-catalyzed production of 6-aminopenicillanic acid (6-APA)

waste as well as milder reaction conditions, it was explained that the biocatalytic process had completely replaced the traditional deacylation route. Similar examples available in other publications emphasize the greenness of biocatalysis [44, 45], as well as its increased use in industry [46, 47].

2.1.5 100 % Atom Economy: Above and Beyond

Since atom economy reflects the intrinsic efficiency of a balanced chemical reaction, it is often conceptually isolated from the wider goals of synthesis and green chemistry. It should be stressed that an ideal atom economy should not deter one from considering other important reaction components, including yield, solvent use, catalyst recovery, energy and toxicity. Rather, an ideal atom economy should be the ultimate goal and the selection standard for achieving the greenest possible process.

As an example, the DuPont adiponitrile synthesis has an atom economy of 100 % (Scheme 2.12). However, the process depends on an equilibrium which favours the formation of the more thermodynamically stable 2-pentenenitrile (2PN). The equilibrium ratio of 3PN/2PN/4PN is 20:78:1.6 respectively [33]. Fortunately, 4PN is the favourable kinetic product [48], and the catalyst ligands can be made bulky to promote formation of the linear 3PN in order to ultimately form adiponitrile in 98 % yield [49]. With a longer reaction time the product yield would be lower.

On many occasions the reaction yield determines the most efficient catalyst and the optimal reaction conditions to be used. A recent article investigating the microwave-assisted multicomponent synthesis of quinolines illustrated the importance of reaction yield [50]. The synthesis of 2,4-diphenylquinoline was shown to be closely dependent on the acidic nature of the catalyst, the temperature inside the microwave, and the reaction time, giving product yields between 10–96 %. Since the atom economy remains fixed regardless of the chosen catalyst and other reaction parameters, it is important to recognize that an atom economy analysis will not always determine the greenest approach.

Although the chemical industry places great emphasis on reaction yield, a multi-metric analysis is often more appropriate for studying the efficiency and greenness of a synthesis. The 2009 article describing K60 silica-catalyzed amide bond forming reactions illustrates this point [28]. Included is a multi-metric comparison between four catalysts in the synthesis of 4,N-diphenylbutyramide. Accordingly, this approach shows that due to a high atom economy and a tenfold reduction in overall waste (as measured by the E factor), the efficiency of the K60 silica catalyzed process overshadows its good product yield.

In concluding the section on atom economy, it is appropriate to consider Trost's 1995 statement concerning his hopes for the future of green chemistry and the metric he proposed. "As the legitimate concerns of society for wise use of our limited resources with minimal environmental risk grow, the ability to produce the chemicals needed to improve the human condition will hinge on the inventfulness of chemists to design more efficient syntheses" [2].

2.2 Reaction Mass Efficiency (RME)

2.2.1 History and Development

The first article of the journal *Green Chemistry* (published in 1999) outlined the importance of metrics in identifying and meeting the challenges of sustainability [51]. This paper was significant as it marked the first time the term "mass efficiency" was used to describe green practices. One year later, Steinbach and Winkenbach introduced the term "balance yield" (synonymous with mass efficiency) as a measure of productivity [52]. Calculated as "main product amount" divided by "balance sheet total input", the balance yield was deemed important as it emphasized productivity, rather than waste, as "a key technical goal in industrial production" [52]. This new perspective marked the birth of globally-oriented mass based metrics which accounted for both the intrinsic and experimental aspects of a chemical reaction. Shortly after these developments, chemists introduced metrics such as mass index [53] (known today as process mass intensity, Chap. 3) as well as clearly-defined equations for reaction mass efficiency [6, 8, 54–61].

2.2.1.1 A Good Start: The Curzons Definition

In 2001, researchers from GlaxoSmithKline (GSK) presented a list of green metrics used by their company to promote sustainable development [54]. Among these, reaction mass efficiency (RME) was emphasized as a realistic metric for describing the greenness of a process. Calculated as product mass divided by the sum of the masses of reactants appearing in the balanced chemical equation [6, 54], it was eventually recognized that RME accounts for yield, stoichiometry and atom economy. This important connection can be drawn by considering a generic reaction
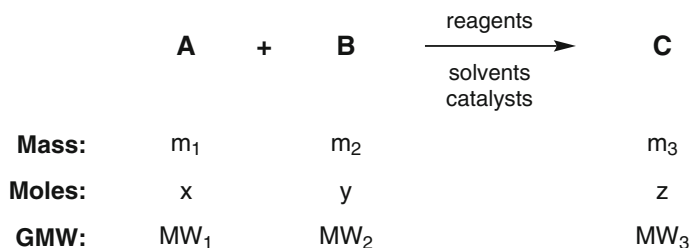
Fig. 2.3 Generic addition reaction where it is assumed that reactant B is in excess (i.e. y > x)


Fig. 2.4 Derivation of reaction mass efficiency as the product of yield, atom economy and the inverse of a stoichiometric factor according to the Curzons definition

(Fig. 2.3) where an excess amount of reactant B is added to reactant A to form product C. Using this example, the Curzons reaction mass efficiency is derived in Fig. 2.4.

The Curzons RME is therefore equivalent to a mathematical product consisting of yield, atom economy and the inverse of a stoichiometric factor, a term introduced by Andraos to measure reactant excess [57–59]. It is worthwhile to check this derivation via Curzons' own example (Scheme 2.18) [54].

Here, it is given that 10.81 g of benzyl alcohol reacts with 21.9 g of *p*-toluenesulfonyl chloride to form 23.6 g of the sulfonate ester. Applying the equation derived in Fig. 2.4 results in a matching RME value of 0.72 for the reaction. Note that the values of yield, atom economy, stoichiometric factor and RME are expressed in absolute form (i.e. as a value ranging between 0 and 1). This is done to make the RME product meaningful. Percent values cannot achieve this, and are therefore omitted for the remainder of the chapter. Understanding the Curzons RME as a product of distinct terms is important as it allows for developing more rational optimization strategies when deciding how to improve the greenness of a process.

Reaction scheme with values:
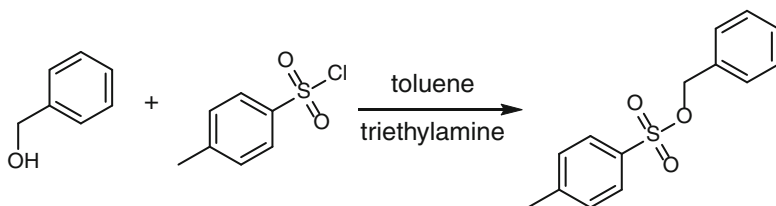
Mass:	10.81 g	21.9 g	23.6 g
Moles:	0.10	0.115	0.09
GMW:	108.14	190.64	262.32

$$\text{RME} = \frac{23.6}{10.81 + 21.9} = 0.72 \qquad\qquad \text{Yield} = \frac{0.09}{0.10} = 0.90$$

$$\text{Atom Economy} = \frac{262.32}{190.64 + 108.14} = 0.88$$

$$\text{Stoichiometric Factor} = 1 + \frac{(0.115 - 0.10) \times 190.64}{0.10 \times (108.14 + 190.64)} = 1.10$$

$$\text{RME} = \text{Yield} \cdot \text{AE} \cdot \frac{1}{\text{SF}} = 0.90 \times 0.88 \times (1.10)^{-1} = 0.72$$

Scheme 2.18 Two calculations of the Curzons RME for the esterification of benzyl alcohol and *p*-toluenesulfonyl chloride [52]

Curzons et al. further justified their metric using cost comparison models for drug manufactures at GSK [6]. Using this data they showed that atom economy influences the manufacture cost of pharmaceuticals much less than yield and stoichiometry. Developing a simple method to account for all three variables thus proved valuable for GSK. In subsequent years, Curzon's RME has gained greater appreciation from chemists in research, commercial and educational settings [55–61].

2.2.1.2 A Unifying Concept: The Andraos Definition

A crucial development of the reaction mass efficiency concept came in 2005 through the work of Andraos [57, 58]. In his mathematical treatise on green metrics [57–59], Andraos recognized that mass efficiency should account for all the materials involved in a chemical process, and not simply the reactant and product masses. This includes the mass of catalysts, solvents, and work-up/purification materials. As a result, Andraos proposed a generalized reaction mass efficiency formula which is simply the mass of the desired product divided by the total mass of all input material relevant to the reaction [57]. Using a similar derivation to that shown in Fig. 2.4, one can see that the generalized RME for a reaction can be

broken down into a product of yield, atom economy, the stoichiometry factor and a new component called the material recovery parameter (introduced to account for catalysts, solvents, and work-up/purification materials [59]). Isolating these four terms in absolute form makes it possible to optimize for efficiency by seeking to achieve values of unity for each parameter.

In addition, by placing assumptions on the recovery and recyclability of reaction components, it became possible to identify context-specific RME formulae for a particular process [59]. In this context, the best-case scenario assumes complete recovery of excess reagents, catalysts, solvents and work-up materials. Consequently, the RME (known as the maximum or kernel RME) is simply the product of the reaction yield and atom economy [57, 59]. At the next level, stoichiometry is considered and as a result one obtains the Curzons RME (Fig. 2.4). The remaining RME formulae [59] follow from the various permutations of recovering one or more of the reaction components mentioned previously. These subtleties are highlighted using the Suzuki reaction mentioned at the start of the chapter (Scheme 2.19).

The experimental conditions shown follow a literature procedure and include an average student yield of 67 %, as obtained in a third year undergraduate lab course at the University of Toronto [9, 62]. In this example, the kernel RME is identical to the Curzons RME which means that reagent excess is not present. When the masses of remaining reaction components are included, the RME decreases significantly to 0.0023. To provide some perspective, Fig. 2.5 shows the mass percent distribution
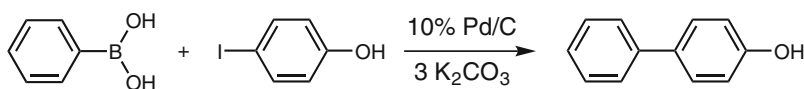
Mass:	0.122 g	0.220 g	0.415 g	0.115 g
Moles:	1.00 mmol	1.00 mmol	3.00 mmol	0.675 mmol
GMW:	121.93	220.01	414.6	170.21

Catalyst Mass: 0.003 g   Reaction Solvent Mass: 11 g

Work-up/Purification Material Mass: 38.1 g

Atom Economy = 0.225   **Yield = 0.675**

Kernel RME = 0.225 x 0.675 = 0.152

$$\text{Curzons RME} = \frac{0.115}{0.122 + 0.220 + 0.415} = 0.152$$

$$\text{Generalized RME} = \frac{0.115}{0.122 + 0.220 + 0.415 + 0.003 + 11 + 38.1} = 0.0023$$

Scheme 2.19 Reaction mass efficiency calculations for the Suzuki reaction using typical results obtained by undergraduate third year students at the University of Toronto [9, 62]
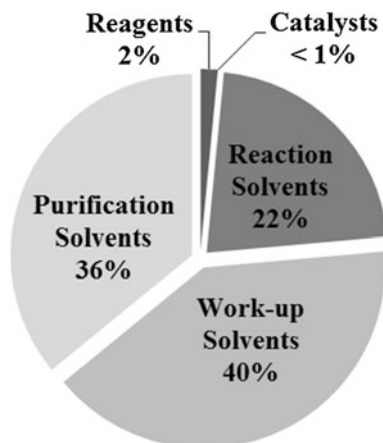
Fig. 2.5 Mass distribution profile of a Suzuki reaction

profile of the Suzuki reaction. With solvents occupying 98 % of the mass involved in the experiment, the decrease between the Curzons RME and the generalized RME becomes understandable.

Although previous reports on the Suzuki reaction demonstrated the recycling of the palladium catalyst [63], catalyst recovery has a negligible effect on the generalized RME. On the other hand, eliminating all solvents would increase the RME by a factor of 65. This analysis highlights the opportunities for optimizing the efficiency of the Suzuki reaction. Finally, the Andraos equations become valuable when experimental masses are not reported in the literature. Expressing the RME as a mathematical product involving reaction yield (routinely reported) and atom economy (easily calculable) enables a simple evaluation when determining the merits for why or why not a certain process might be considered green.

2.2.2 Applying RME to Catalysis

The synthesis of 2,4-diphenylquinoline (Sect. 2.1.5) showed that atom economy is limited in its potential to measure process efficiency [50]. Improving an atom economy of 93 % given reaction yields below 50 % will accomplish little in terms of achieving productivity and efficiency. In this section, the reaction mass efficiency metric will be used to provide a more global and robust perspective on greenness and sustainability.

2.2.2.1 Mass Efficiency in Heterogeneous Catalysis

In a recent article, Mercer et al. analyzed five industrial routes for the conversion of benzene into aniline [24]. The fifth and most efficient process (Scheme 2.20) included two steps: nitration of benzene via electrophilic substitution followed by
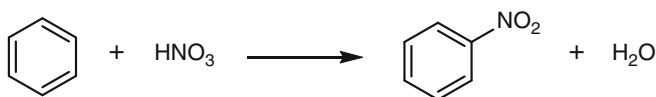
Mass: 589.7 kg   480.8 kg   907.2 kg (98% yield)
GMW: 78.11   63.01   123.11
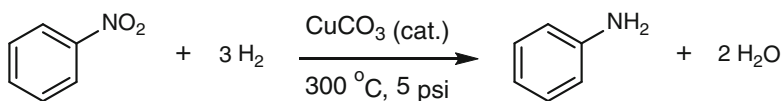
Mass: 907.2 kg   >43.6 kg   671.3 kg (98% yield)
GMW: 123.11   6.05   93.13

Catalyst Mass: 5.03 kg   Reaction Solvent Mass: 654.1 + 98.9 = 753 kg

Work-up and Purification Material Mass: 9.1 kg

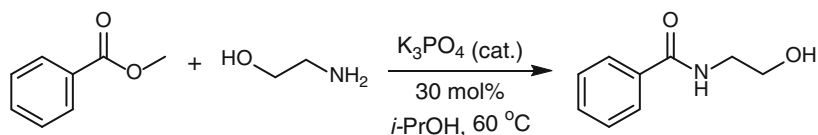**Atom Economy = 0.63   Yield = 0.96**

Kernel RME = 0.63 x 0.96 = 0.605

$$\textbf{Curzons RME} = \frac{671.3}{589.7 + 480.8 + 43.6} = 0.603$$

$$\textbf{Generalized RME} = \frac{671.3}{589.7 + 480.8 + 43.6 + 5.03 + 753 + 9.1} = 0.357$$

Scheme 2.20 Reaction mass efficiency calculations for the industrial conversion of benzene to aniline [24]

the familiar hydrogenation of nitrobenzene which is catalyzed by $CuCO_3$ on silica (Sect. 2.1.4.1). To evaluate this synthesis by means of RME, a 46.3 kg mass of H_2 is introduced as the minimum amount of hydrogen needed to produce the 671.3 kg of aniline quoted in the article. A kernel RME of 0.605 is thus calculated for the process. This value decreases slightly when stoichiometry is included. Accounting for all process components further reduces the RME by 41 %. The generalized RME is much greater than that of the Suzuki reaction, which is understandable since industrial processes generally need to be much more efficient than laboratory preparations. To put this into perspective, according to a recent estimate, few synthetic schemes with more than four steps achieve general RME values above 0.15 [8]. The mass distribution for this process is divided between reagents (58 %) and reaction solvents (41 %), with catalysts and work-up/purification materials representing small quantities by comparison. This distribution further highlights the mass efficiency that is typical of industrial processes (Scheme 2.21).

Mass: 192.2 mg   86.9 mg   188.3 mg

Moles: 1.42 mmol   1.42 mmol   1.14 mmol

GMW: 136.15   61.08   165.19

Catalyst Mass: 90 mg   Reaction Solvent Mass: 550 mg

Atom Economy = 0.84   **Yield = 0.80**   **Kernel RME = 0.674**

$$\textbf{Curzons RME} = \frac{188.3}{192.2 + 86.9} = 0.674$$

$$\textbf{Generalized RME} = \frac{188.3}{192.2 + 86.9 + 90 + 550} = 0.205$$

**Scheme 2.21** Reaction mass efficiency calculations for a base-catalyzed ester amidation [64]

2.2.2.2 A Homogeneous Base-Catalyzed Amidation

Optimization of a base-catalyzed ester amidation has been described recently by
Caldwell et al. [64]. The authors started with a base-mediated transesterification
between an ester and an amino alcohol, which, upon rearrangement, gave the more
thermodynamically stable amido alcohol product. Using catalyst and solvent
screening, it was established that potassium phosphate in isopropanol had the
highest product conversion. Moreover, reaction yield and the Curzons RME were
used as metrics to show that the reaction achieved an average RME of 70 %, which
was higher than a previously published report [54]. An example reaction
(Scheme 2.23) shows that the kernel RME matches the Curzons RME meaning that
no excess reagents were used.

In addition, incorporating the solvent and catalyst masses decreases the RME by
70 %. Since the catalyst represents 10 % of the entire mass distribution for this
reaction, exploring catalyst recycling in future studies might result in an improved
overall RME.

2.2.2.3 Biocatalysis and the Synthesis of 7-ACA

7-Aminocephalosporanic acid (7-ACA) constitutes a crucial precursor to many
important semi-synthetic antibiotics including cephalosporins. In 2008, global 7-ACA
production exceeded 6,000 tonnes with a market value of over US$400 million [65].
7-ACA has been traditionally made by a four-step chemical route first developed in
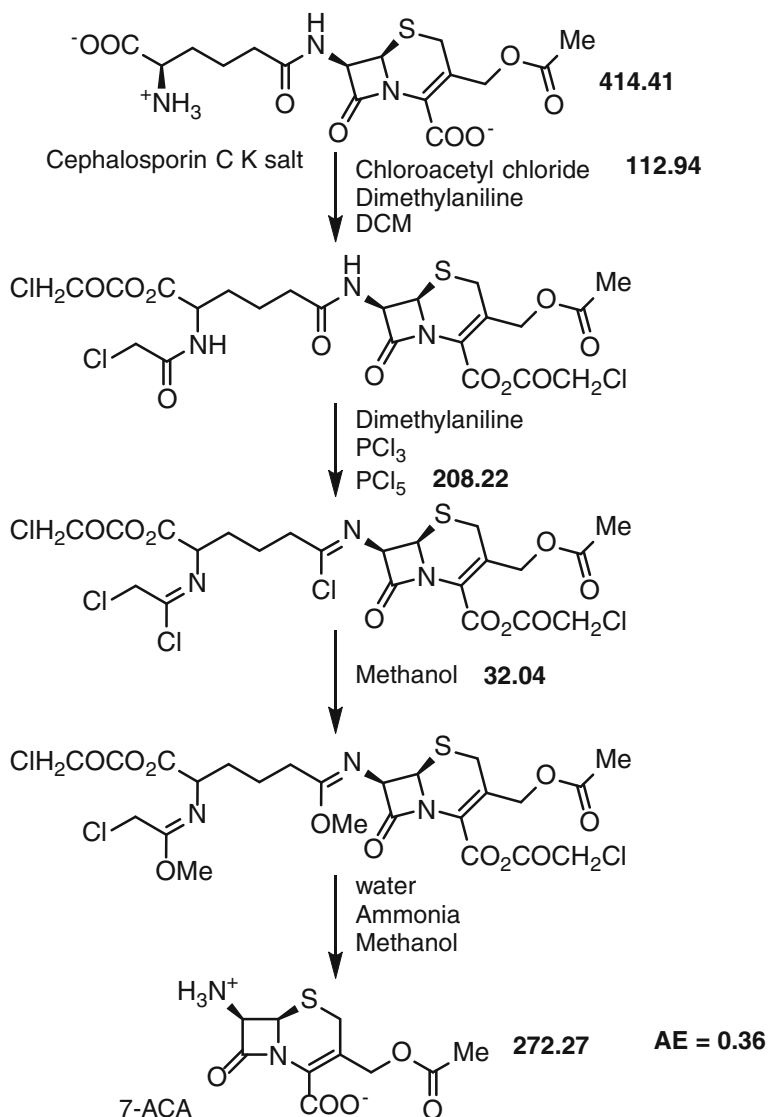
Scheme 2.22 Atom economy of the chemical route to 7-ACA [65]

1980 (Scheme 2.22) [66]. The process starts with acyl chloride protection of the amine and carboxylic acid groups of the potassium salt of cephalosporin C forming a mixed anhydride. This is then treated with phosphorus pentachloride to make an imodyl chloride which undergoes enol ether formation when treated with methanol. The resulting imodyl ether then hydrolyzes with water to give 7-ACA as the final product with an atom economy of 36 %.
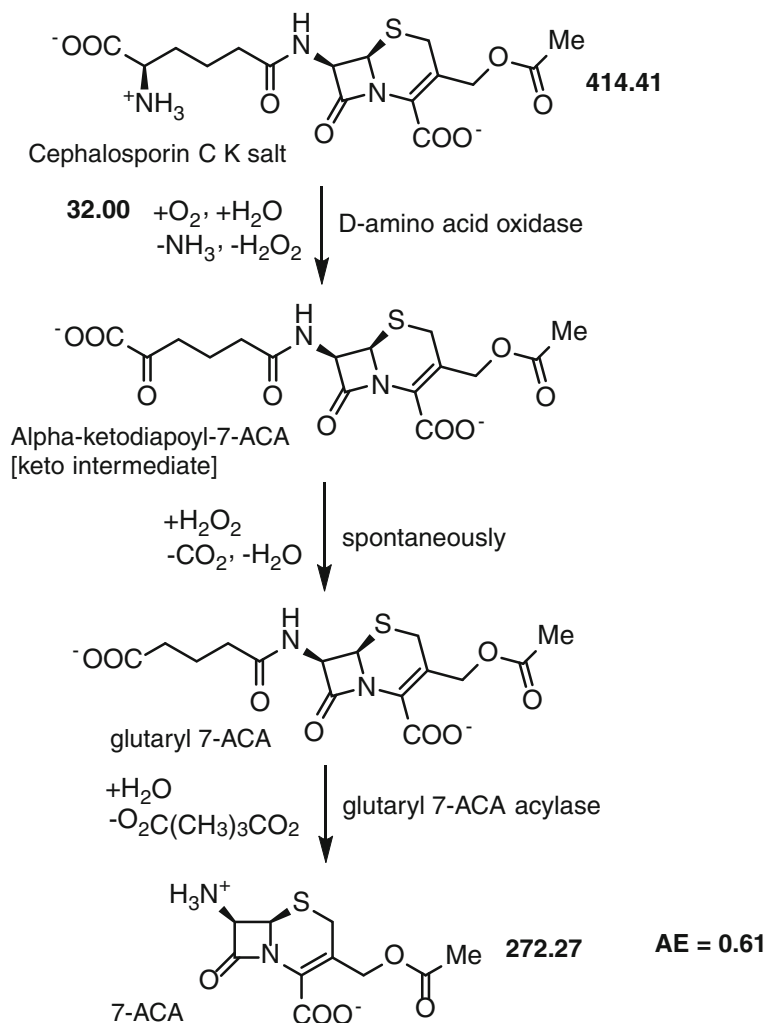
**Scheme 2.23** Atom economy of the biocatalytic route to 7-ACA [65]

In comparison, the biocatalytic synthesis (Scheme 2.23) proceeds with an atom economy of 61 %. This route has completely replaced the chemical process, largely due to its 90-fold reduction in overall waste and seven-fold reduction in solvent emissions [65, 67]. Starting with a solution of the cephalosporin C potassium salt stirred with immobilized D-amino acid oxidase (DAO), reaction with oxygen gas (added via compressed air) produces a keto intermediate and hydrogen peroxide as byproduct. These then react spontaneously to form glutaryl 7-ACA which is separated from DAO (recycled) and stirred in the presence of glutaryl 7-ACA acylase (GAC) to give 7-ACA.

Table 2.1 Efficiency metrics values comparing the chemical and biocatalytic synthesis of 7-ACA calculated using RME formulas and information provided in reference [65]

Efficiency metrics	Chemical route	Biocatalysis route
Atom economy	0.355	0.610
Molar yield	0.750	0.670
Actual yield (kg)	1	1
Mass of raw materials excluding water (kg)	81	44
Reactant mass (kg)	7	3
Kernel RME	0.2663	0.4087
Curzons RME	0.1429	0.3333
Generalized RME excluding water	0.0123	0.0227
E factor including water	93	172
Generalized RME including water = $(E \ factor + 1)^{-1}$	0.0106	0.0058
Solvent mass excluding water (kg)	74	41
Mass of water used (kg)	13	129

A 2008 study by Henderson et al. compared these two processes according to several criteria including green metrics [65]. Combining the results of the analysis, the atom economies and several simple equations relating RME with the E factor and process mass intensity (Chap. 3), one can determine the relevant reaction mass efficiency values for these two processes (Table 2.1). Surveying these values shows that the biocatalysis route is more efficient in terms of material use when water is excluded from the measurements. Interestingly, the inclusion of water reduces the generalized RME of the biocatalysis route by 75 %.

The kernel and Curzons RMEs for this route are 53 and 133 % respectively higher than for the chemical route, clearly indicating that the biocatalysis process is more efficient. Future research should therefore aim to reduce the amount water used in the process. The mass distribution profiles for the two routes are illustrated in Fig. 2.6.
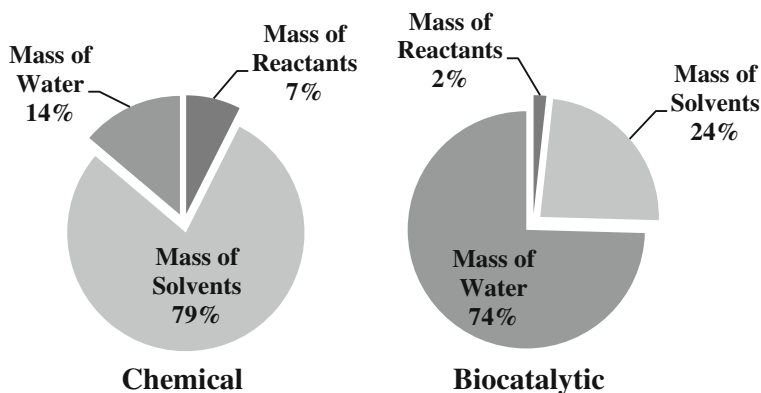
Fig. 2.6 Mass distribution profiles for the chemical and biocatalytic routes to 7-ACA
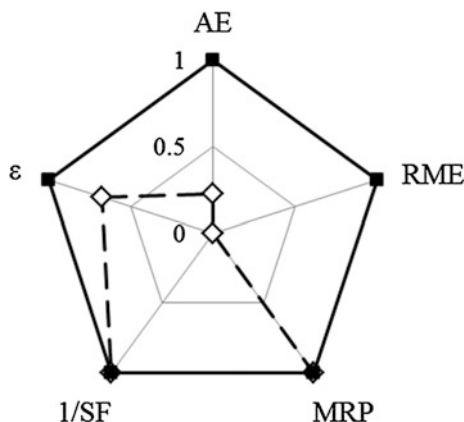
Fig. 2.7 Radial pentagon representing RME values for a Suzuki reaction

2.2.3 Future Directions

With multiple process parameters being tracked by reaction mass efficiency, organizing all the information in an intelligible manner may appear daunting. To aid with this problem, Andraos has proposed the visual model of a radial pentagon [8, 59]. Essentially, a pentagon is used to assign key reaction mass efficiency terms (atom economy, yield, RME, SF, MRP) at each corner. Assigning the edges a value of 1 and the center a value of 0 allows tracking of all five terms simultaneously along the contour of the pentagon. Points are then drawn where appropriate, and connecting adjacent points provides an immediate overall picture of how close (or far) from ideality the process is (the ideal process being represented by the perimeter of the pentagon). With this visual aid it is possible to quickly determine which terms contribute to a low RME. For example, Fig. 2.7 shows the pentagon analysis of the Suzuki reaction discussed in Sect. 2.2.1.2. One of the virtues of this approach is that it is easily extended when one introduces additional metrics with values ranging between 0 and 1.

Along with these tools, the work of Andraos includes creating process cost and energy models [68], defining environmental impact parameters on the basis of a radial polygon approach [61], predicting the intrinsic greenness of reactions given appropriately chosen thresholds [69], and creating a database of intrinsically green reactions [70].

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