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Molar Efficiency: A Useful Metric To Gauge Relative Reaction Efficiency in Discovery Medicinal Chemistry

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Supporting Information

ABSTRACT: The concept of molar efficiency is introduced as a new metric to enable assessment of reaction efficiency in discovery medicinal chemistry. Calculations from molar units enable cross-comparison of the broad range of transformations employed in discovery-phase medicinal chemistry research and is proposed to facilitate identification of more sustainable synthetic transformations.

$$\text{Molar Efficiency (Mol. E) \%} = \frac{\text{moles Pdt}}{\text{moles SM+Add.+Cat.(+Solv.)}} \times 100$$

Pdt = product
SM = starting materials
Add. = additives
Cat.= catalysts
Solv. = solvent

KEYWORDS: *Metrics, Discovery medicinal chemistry, reaction efficiency*

INTRODUCTION

The issue of sustainability within the chemical industry is a topic of increasing importance from small-scale discovery to large-scale development and is necessary in order to mitigate the impact of current activities on the environment and resource availability, while endeavoring to ensure the longevity of manufacturing processes.[1−4] In the context of the pharmaceutical industry, there is a strong desire to embed sustainable principles earlier in the drug discovery process, specifically within discovery-phase medicinal chemistry.[5] It has been recommended that sustainable practices are adopted more extensively within medicinal chemistry with the anticipation that this will have both a beneficial impact on the general efficiency of a particular program and subsequent knock-on effects upon synthetic activities associated with compound progression through initial large-scale synthesis (e.g., for extended in vivo and toxicological studies at the candidate selection stage) and subsequently into the development (process chemistry) phase.[5]

In 1998, Anastas and Warner introduced the *12 Principles of Green Chemistry* as a guide to designing the ideal chemical process, which maximizes productivity while minimizing waste production.[4] In this regard, the use of mathematical expressions with numerical outputs has emerged as a convenient method for quantifying the efficiency of a particular chemical transformation and thus providing a measure of sustainability.[6−15] Indeed, a number of metrics have been developed, each with specific outputs that inform on a range of aspects of a particular reaction. Examples of these are as follows: Atom Economy (Trost, 1991),[16] E-Factor (Sheldon, 1992),[17,18] Environmental Quotient (Sheldon, 1994),[17] Effective Mass Yield (Hudlicky, 1999),[19] Process Mass Intensity (Curzons 2001),[20] Reaction Mass Efficiency (Curzons 2001),[20] Carbon Efficiency (Curzons, 2001),[20] Life Cycle Assessment,[21] Energy Efficiency (Clark, 2005),[22] Material Recovery Parameter (Andraos, 2005),[23,24] and Global Material Recovery (Auge, 2012).[25]

These metrics can be considered as two classes: those that inform on environmental impact (e.g., environmental quotient and LCA) and those that largely inform on the efficiency and waste generation (the remaining metrics). Of these selected metrics, atom economy (AE),[16] E-Factor,[17,18] process mass intensity (PMI),[20] and reaction mass efficiency (RME)[20] are perhaps the most widely utilized (Table 1). Developed by Trost in 1991, AE serves to determine the efficiency of a chemical reaction with regard to how many atoms from the starting materials reside within the product. AE disregards the yield of the reaction and has an ideal value of 100%, i.e., all atoms from the starting materials reside in the product. In 1992, Sheldon introduced the more comprehensive E-Factor matrix, which compares the mass of product to the mass of waste produced for a given process. E-Factor takes into account all raw materials and waste associated with a transformation or sequence, including any associated purification steps, with the

Table 1. Definitions of AE, E-Factor, MI, and RME

metric	equation	aim (ideal value)
AE[16]	MW of product/$\sum$(MW of stoichiometric reactants) × 100	increase (100%)
E-Factor[17,18]	mass of waste/mass of product	decrease (0)
PMI[20]	$\sum$(mass of stoichiometric reactants + solvent)/mass of product	decrease (1)
RME[20]	mass of product/$\sum$(mass of stoichiometric reactants) × 100	increase (100%)

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$$\text{Molar Efficiency (Mol. E) \%} = \frac{\text{moles Pdt}}{\text{moles SM+Add.+Cat.(+Solv.)}} \times 100$$

Pdt = product
SM = starting materials
Add. = additives
Cat.= catalysts
Solv. = solvent

Figure 1. Equation for molar efficiency calculations.

ideal overall synthetic process registering a value of zero. It should be noted that a variety of less inclusive E-Factor calculations (e.g., based solely on the stoichiometric equation) can also be used for a more convenient analysis.[3] A decade later, in 2001, Curzons and co-workers disclosed the PMI and RME metrics, both of which relate the mass of components employed in a reaction to the mass of desired product formed. RME compares the mass of desired product to the total mass of all stoichiometric reagents and, like AE, has an ideal value of 100%. Similarly, PMI compares masses of reactants to product but does account for the solvent used in a process resulting in an ideal value of 1 kg/kg.

These metrics have been broadly useful as methods with which to assay individual reactions and overall processes. Indeed, indices such as PMI and RME have been instrumental in advancing the sustainability of pharmaceutical processes, with PMI highlighted as "...the preferred metric aimed to drive greater efficiencies in pharmaceutical syntheses."[26,27] However, it has been observed that there is no universal metric to compare and contrast all chemical processes against each other due to limitations in the current calculations.[9] For example, it is frequently difficult to know exactly which components of a reaction should be included in a specific calculation as a broad array of inputs are both useful and required for a wide range of purposes. The ambiguity over what aspects of a given transformation should be evaluated is not necessarily a negative point; rather, this is perhaps one of the most useful aspects of evaluation via efficiency metrics as it can inspire debate that may lead to increased engagement with the central theme of sustainability.

In this regard, our interest in the area of sustainable synthesis in discovery-phase medicinal chemistry[28−31] has led us to develop an alternative metric based on molar efficiency, which we believe offers the potential to offer additional insight into the efficiency of reactions. We believe this new metric has certain advantages that may provide an additional level of analysis, particularly within discovery chemistry. In particular, it enables different classes of reaction, as well as subtleties within one particular reaction manifold, to be compared and contrasted comprehensively. This may increase engagement and encourage further debate over the efficiency of the staple processes of synthetic chemistry in this widely practiced area.

DISCUSSION

Discovery-phase medicinal chemistry typically involves the routine use of a large number of a wide variety of small-scale reactions to efficiently access target compounds. To assist in the identification of reactions that pose issues in terms of their sustainability and assist in the development of new more effective synthetic transformations, we sought to compare the efficiency parameters of a variety of commonly used methodologies. However, at the outset of this work, we quickly realized that while many of the established metrics are extremely useful in gauging improvements in the net efficiency of one specific reaction under varying conditions and/or on varying scale, comparing and contrasting different types of reactions to one another is more complicated. For example, although AE is quick and straightforward to calculate, it ignores stoichiometry as well as any catalyst, additives, or solvent used in the reaction and also does not factor the reaction yield. Similarly, while RME does adjust for chemical yield, it too ignores certain additives as well as the solvent used in the reaction. E-Factor is without doubt the more comprehensive evaluation; however, the waste from a reaction can be difficult to quantify thus making it a less practical metric to use on a day-to-day basis in situations where a large number of small-scale reactions are being performed, such as within discovery chemistry where recording the quantities of workup/purification solvents, etc., is not routine.[5] However, and as intimated above, it is possible to use a less holistic E-Factor calculation based on a lower number of included variables to gain a series of alternative insights.[3] Analogously, PMI and other metrics of high-value in process research chemistry such as life cycle analysis (LCA), simply are not practical in this high-throughput small-scale setting, where the requisite data is frequently not captured.

In terms of E-Factor, PMI, and RME, the major difficulty experienced in endeavoring to compare and contrast the efficiency outputs from a series of different reactions stemmed directly from the units employed for these calculations: These metrics are based on the input and output of *mass* of material (starting material, products, waste, etc.). The mass of one specific reagent is not necessarily equivalent to another, i.e., the molecular weights of reagents are nonequivalent and therefore not commutable. As stated above, when seeking to compare the variance in efficiency between conditions set, for example, for individual runs of a batch process, E-Factor, PMI, and RME are excellent evaluation metrics. However, these analyses are less suited to the comparison of different types of reaction where the chemical inputs and outputs are nonuniform. For example, 10 mL of *n*-hexane has a mass of 6.55 g, while 10 mL of CH_2Cl_2 has a mass of 13.3 g; physical variations such as this may render comparison of reactions with different inputs or conditions difficult, possibly giving misleading results.

In order to enable the comparison of different types of reaction so as to provide a guide to the most effective methods for a particular bond construction, we believe an efficiency calculation based on molar units would be useful. Molar units are universal across all chemicals and are readily available. A reaction efficiency based on moles of inputs and outputs would potentially give a useful alternative representation of the incorporation of starting materials into desired product while enabling an effective account of the impact of chemical yield and, where desired, solvent could also be included.

The proposed expression for this calculation is simply represented in Figure 1.

All of the components required for a transformation to proceed are included (in contrast to some other metrics, such as AE and RME), with the resulting value (expressed as a %) indicating the efficiency of transforming the starting materials into product under the chosen conditions. For example, 100%

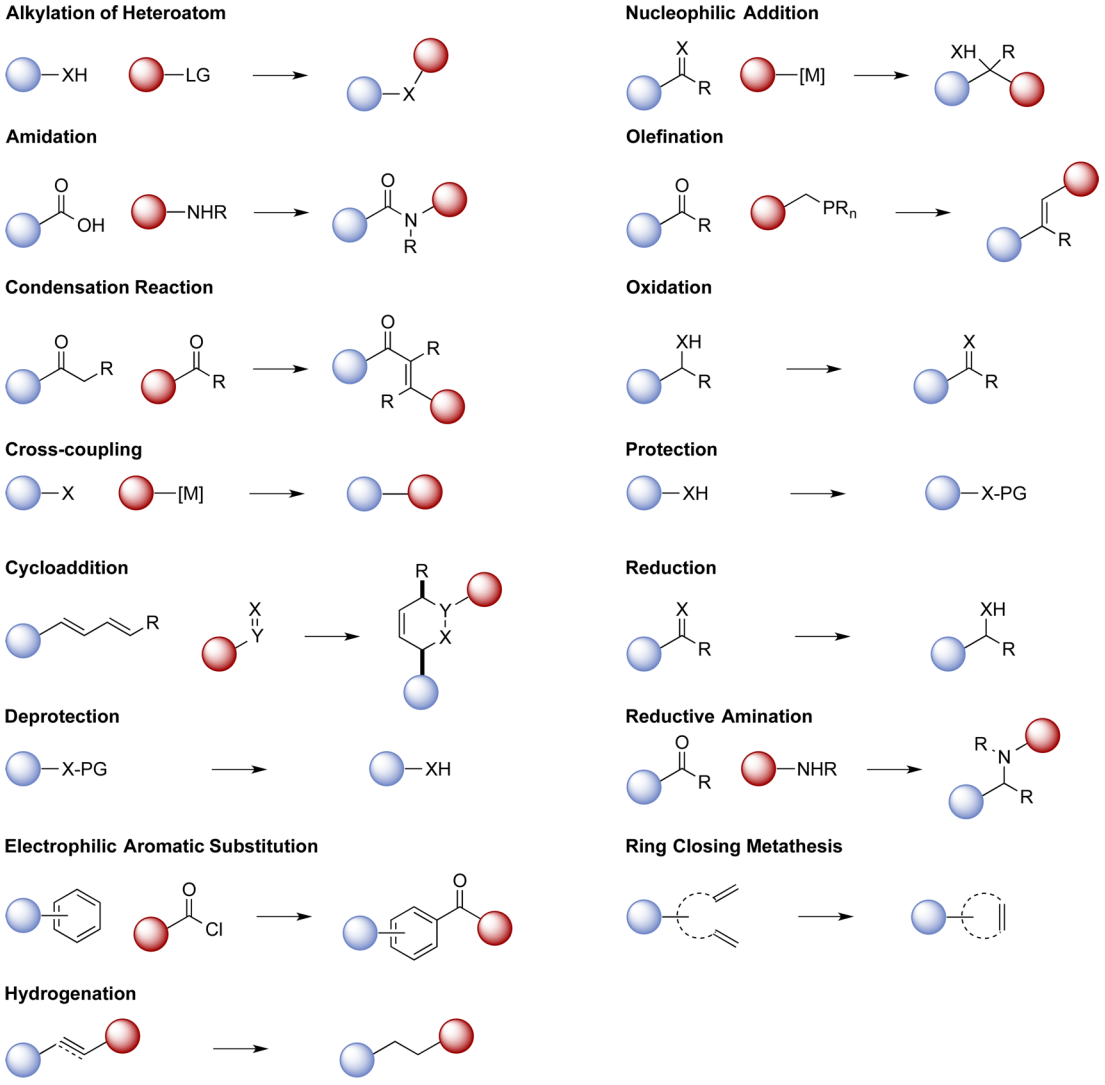

Figure 2. General Markush sketches of reactions analyzed in Table 2. For more information on the specific reactions and associated conditions, see the Supporting Information.

molar efficiency could be achieved in a reaction in which two starting materials react in 1:1 stoichiometry, in the absence of additives, catalysts, or solvent (i.e., neat), to give the desired product in 100% yield. While the majority of reactions do require solvent in order to effectively proceed, this imparts greater efficiency values to reactions that are performed at higher concentrations (vide infra). Furthermore, greater efficiencies are achieved with reactions that avoid undesirable or wasteful ratios of starting materials or reagents/catalysts.

To illustrate the practical use of molar efficiency versus AE, E-Factor, MI, and RME, we analyzed three examples of 15 common classes of synthetic transformations that have been identified by MacDonald[32] and Roughley[33] as being frequently used in discovery-phase medicinal chemistry (with the exception of cross-coupling where we elected to analyze five of the most prevalent reaction manifolds). These were taken from the recent literature in order to ensure that the synthetic methodology being used would be as contemporary as possible and are listed in Figure 2 and Table 2 along with the associated efficiency calculation values based on the available experimental data.

As anticipated, insufficient experimental data was provided to enable calculation of a complete E-Factor or PMI for any of the selected transformations. This is attributable to the fact that recording the quantity of aqueous solutions, extraction solvents, drying agents, silica, eluents, etc. is not typical to discovery-phase chemistry. This highlights that despite being broadly useful within process research chemistry, E-Factor and PMI are generally not as accessible for day-to-day use within a discovery laboratory. However, for comparison, we have included a restricted E-Factor analysis based on only the available data (masses of reagents, catalysts, additives, solvents, and products).[3] We elected to evaluate two different representations for both the restricted E-Factor and Mol. E metrics, which can offer alternative views of the transformation under review; these were based on the exclusion or inclusion of the solvent.

From the calculated data, a series of observations could be made: (i) It was clear that AE gives a very idealized view of a particular transformation in that, while it provides an indication as to the reaction efficiency based on atom incorporation, this is more a qualitative illustration of the reaction class and of limited practical value.

(ii) The restricted E-Factor calculation (without solvent) effectively demonstrates the variability in efficiency of the reaction classes under analysis. Not only does the general efficiency vary from class to class, but also, the specific

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Table 2. Calculations of AE, E-Factor, RME, and Mol. E for Representative Examples of Reactions Commonly Used in Discovery-Phase Medicinal Chemistry[a]

entry	reaction class	*n*	AE (%)[b]	E-Factor[c]	RME (%)[d]	Mol. E (%)[e]	ref
1	alkylation of heteroatom	a	96	3.0 (10)	25	14 (2.0)	34
		b	83	7.2 (42)	12	5.7 (0.50)	35
		c	77	2.8 (28)	27	15 (0.56)	36
2	amidation	a	96	6.6 (69)	13	6.2 (0.28)	37
		b	96	1.7 (14)	37	18 (1.3)	38
		c	89	3.6 (20)	22	11 (0.91)	39
3	condensation reaction	a	96	4.4 (90)	19	6.1 (0.12)	40
		b	85	1.3 (46)	54	22 (0.24)	41
		c	80	1.4 (21)	42	18 (0.97)	42
4	cross-coupling	a	72	3.7 (20)	22	14 (1.1)	43
		b	71	17 (209)	6.0	4.3 (0.12)	44
		c	81	4.9 (51)	18	7.5 (0.44)	45
		d	71	2.6 (15)	29	13 (1.6)	46
		e	86	2.0 (43)	36	12 (0.21)	47
5	cycloaddition	a	100	0.35 (16)	74	36 (1.3)	48
		b	100	0.78 (45)	56	32 (0.52)	49
		c	100	2.2 (49)	31	11 (0.36)	50
6	deprotection	a	79	0.80 (19)	56	6.2 (0.40)	51
		b	75	3.5 (21)	22	18 (1.1)	52
		c	76	91 (106)	1.1	0.0053 (0.0052)	53
7	electrophilic aromatic substitution	a	86	5.6 (91)	15	8.3 (0.41)	54
		b	91	2.2 (10)	31	11 (2.3)	55
		c	90	1.9 (5.4)	34	18 (6.0)	56
8	hydrogenation	a	100	500 (632)	0.20	0.0012 (0.0011)	57
		b	100	282 (310)	0.35	0.0026 (0.0026)	58
		c	100	704 (966)	0.14	0.00010 (0.00010)	59
9	nucleophilic addition	a	90	0.87 (6.2)	54	26 (2.3)	60
		b	66	4.4 (45)	19	13 (0.54)	61
		c	78	0.39 (41)	72	47 (0.50)	62
10	olefination	a	49	7.3 (110)	12	7.9 (0.17)	63
		b	61	1.2 (5.8)	46	31 (5.3)	64
		c	58	1.6 (10)	38	23 (3.7)	65
11	oxidation	a	100	1.9 (111)	34	26 (0.19)	66
		b	99	4.4 (68)	18	7.3 (0.39)	67
		c	100	0.74 (12)	58	47 (1.1)	68
12	protection	a	73	1.1 (6.5)	49	32 (5.2)	69
		b	93	0.58 (31)	64	25 (0.57)	70
		c	78	1.2 (9.8)	46	27 (1.9)	71
13	reduction	a	85	4.1 (17)	20	5.1 (1.3)	72
		b	92	1.5 (198)	40	6.7 (0.050)	73
		c	82	0.31 (5.7)	77	41 (3.3)	74
14	reductive amination	a	58	2.0 (7.8)	33	17 (3.8)	75
		b	51	1.5 (10)	39	26 (3.6)	30
		c	69	2.5 (15)	29	6.8 (0.68)	75
15	ring closing metathesis	a	93	0.20 (152)	88	86 (0.15)	76
		b	91	0.18 (447)	89	81 (0.064)	77
		c	94	1.3 (483)	48	42 (0.045)	78
	average		**84**	**36 (101)**	**35**	**20 (1.2)**	

[a]Data represented to two significant figures. [b]Calculated using the equation from Table 1 using the stoichiometric reactants that reside in the product. [c]Calculated using the equation from Table 1 including all reactants and only the product output; no workup or purification contributors were used. Values in parentheses include solvent. [d]Calculated using the equation from Table 1 with inclusion of all stoichiometric reagents. [e]Calculated using the equation from Figure 1. Values in parentheses include solvent.

efficiency of exemplars within each class could vary broadly. For example, the restricted E-Factor calculations for the amidation reaction class (Table 2, entry 2), the most prevalent reaction class as illustrated by MacDonald[32] and Roughley,[33] ranges from 1.7 to 6.6, i.e., a variability of a factor of approximately four. This restricted E-Factor calculation gives an output that closely resembles the reciprocal of RME (expressed as a fraction) across the data set; the contribution of the catalytic components to the restricted E-Factor was of low significance. Accordingly, the observed trends were similar.

(iii) From further consideration of the individual reaction classes, it was apparent that some heterogeneity existed in the

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efficiencies of specific exemplars, which could largely be attributed to the concentration at which the reaction was conducted. This was not a localized effect within particular reaction classes that are generally known to require increased dilution, such as ring closing metathesis processes (Table 2, entry 15), but was demonstrated globally and was indicative of a wide range of concentrations being employed across the data set examined. The inclusion of solvent into the restricted E-Factor calculation therefore gave further detail with the expected trend, i.e., reactions run under more dilute conditions tend to generate poorer efficiency values and vice versa. However, some results were noticeably skewed and this was impacted by both the concentration as well as the associated variability in the density of the solvent. Consequently, and as noted above, given that this equation is based on mass, it became difficult to effectively compare and contrast the classes of reaction as well as the specific examples of each class due to the variance of physical properties of the inputs.

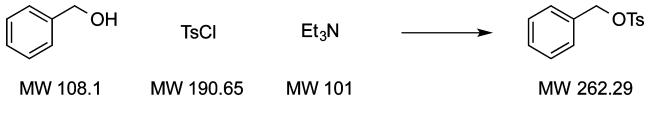
(iv) Mol. E provided a useful alternative view of reaction efficiency, which generally gave lower values than all of the other metrics evaluated. This is perhaps unsurprising when one considers how molecular weight fluctuates between different reagents; an example of this was clearly demonstrated in the results for hydrogenation (Table 2, entry 8). With a molecular weight of 2.02 Da, the effect of a large molar excess of H_2 on mass-based calculations (restricted E-Factor and RME) was significantly less than the effect on Mol. E where the overall contribution of this excess cannot be escaped; the Mol. E calculations for hydrogenation reactions were orders of magnitude lower than the corresponding restricted E-Factor and RME values. Once more, the inclusion of solvent to Mol. E calculations had the expected trend of decreasing the output value. However, the outputs from this calculation were primarily influenced by concentration, as would be expected, with no issues arising over molecular weight/density.

(v) Accordingly, in relation to the average AE, E-Factor, RME, and Mol. E data across the 47 reactions, it was immediately apparent that as the analysis becomes more holistic (i.e., on moving from AE to restricted E-Factor/RME to Mol. E), the average efficiency becomes poorer. As described above, AE tends to provide results that are much more favorable in appearance with the average value of 84%. Upon introduction of more factors into the calculation (all stoichiometric reagents), this falls to 35% for the average RME. This becomes poorer still for restricted the E-Factor (a value of 36) where all stoichiometric and substoichiometric inputs were included and more so (to a value of 101) if the solvent was included. Increasing the granularity of analysis to encompass all stoichiometric and substoichiometric reactants based on molar inputs with and without solvent provides the Mol. E averages of 20% and 1.2%, respectively.

Being more inclusive, the E-Factor and Mol. E calculations with inclusion of solvent are therefore more indicative of the inherent inefficiencies of the synthetic approaches in discovery-phase chemistry. Having stated this, the chemistry used in discovery chemistry reflects the intrinsic efficiency of the fundamental techniques identified from the contemporary literature, which have in general been employed without any specific optimization.

With specific regard to the issue of ambiguity highlighted above, it was noted that during calculations for our study an issue of uncertainty arose over what should be included in the equation for AE: Two different papers calculated two entirely different values for the AE for the same transformation (Scheme 1).[14,20] This inconsistency was due to either inclusion or exclusion of the stoichiometric base (Et_3N).

Scheme 1. Ambiguity Surrounding Inclusion of Stoichiometric Reactants in the Calculation of AE[14,20]



AE (ref. 14): 262.29/(108.1+190.65) x 100 = **87.8**%
AE (ref. 20): 262.29/(108.1+190.65+101) x 100 = **65.8**%

In terms of AE and RME, specific additives are often not included in the calculation. However, for many of the most widely employed reactions, simply stirring a mixture/solution of two reactants in a vessel will not result in a successful bond construction. For example, combining an aryl halide and a boronic acid in solvent will not lead to the corresponding adduct via a Suzuki–Miyaura process; a catalyst, typically Pd(0), is absolutely essential to the success of the cross-coupling event. Moreover, the majority of the reactions surveyed employ excesses of at least one component and usually of several. An example of a Suzuki–Miyaura reaction (Table 2, entry 4a) is given in Scheme 2. In this example, not only is the boronic acid used in excess, the associated base (another typically essential component in such reactions) is also in excess. Consequently, we believe that any entity present in the reaction milieu should be included in the calculation as its presence is fundamental to the successful outcome of the process. This also avoids any issues of ambiguity over what should or should not be included. Once more, ambiguity is possible when employing mass-based calculations to evaluate different examples of a specific reaction: two routinely employed bases for Suzuki–Miyaura cross-coupling are K_2CO_3 and Cs_2CO_3. The associated molecular weights are 138.21 and 325.82, respectively. Accordingly, when all other factors are equal, a reaction employing the same number of equivalents of base will appear more favorable when using K_2CO_3 versus Cs_2CO_3 if a mass-based calculation were employed but is a non-issue when using molar units.

A common reason for omission of catalysts, particularly metal catalysts, from AE and RME is the assumption that these can be recycled and reused after a reaction. However, this is rarely the case, especially in a discovery setting, as many of these metal species are precatalysts and are consequently irrecoverable in their original state (oxidation, ligation, etc.) after use. In addition, life cycle analysis would be necessary to ascertain the benefits of any proposed recycling. For the Suzuki–Miyaura example in Scheme 2, $Pd(OAc)_2$ is a precatalyst that is reduced to the active Pd(0) catalyst in situ to allow the reaction to take place. Consequently, at the end of the reaction, $Pd(OAc)_2$ will not be recovered. While it is possible to recover the Pd residues from the reaction and convert these back to $Pd(OAc)_2$, this will require further processing and will undoubtedly return less than 100% of the original quantity of $Pd(OAc)_2$. This equally applies to a wide variety of metal-based catalysts including metathesis catalysts (e.g., Ru, Mo), catalysts for conjugate addition processes (e.g., Cu, Rh), hydrogenation catalysts (e.g., Ir, Pd, Rh, Ru), and many other systems. Similarly, many of the acidic or basic

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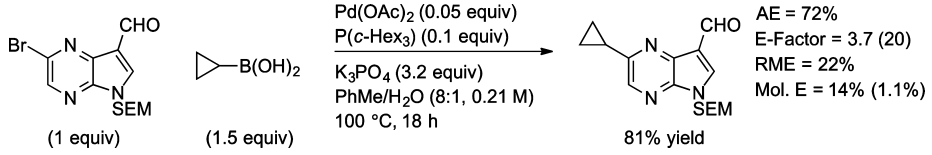
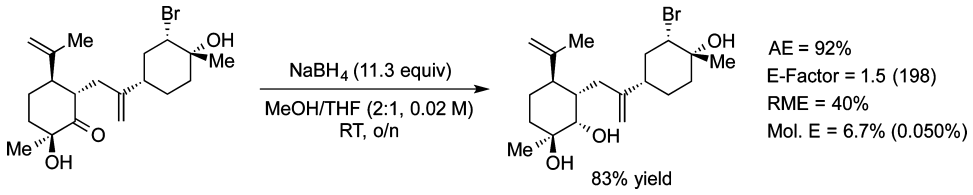
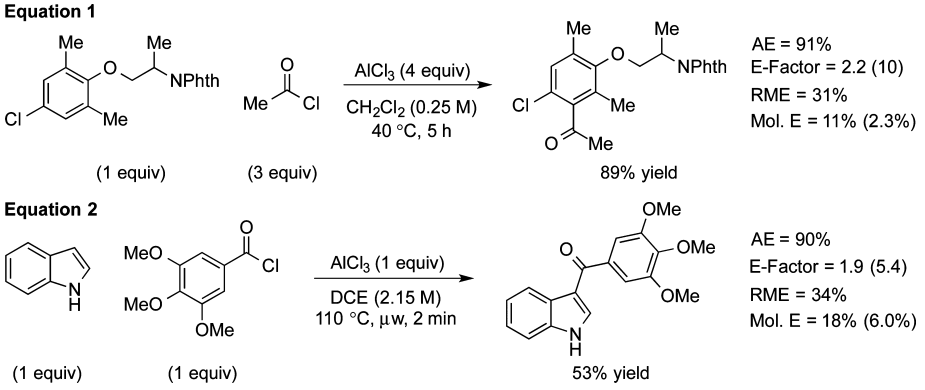
Scheme 2. Example of a Suzuki–Miyaura Reaction and Associated Calculations (Table 2, Entry 4a)



Scheme 3. Example of a Reduction Reaction and Associated Calculations (Table 2, Reaction 13b)



Scheme 4. Examples of Electrophilic Aromatic Substitution Reactions and Associated Calculations (Table 2, Eq 1, Reaction 7b; Eq 2, Reaction 7c)



inorganic catalysts and organic catalysts that have found extensive use in synthetic organic chemistry, particularly within asymmetric catalysis (amine catalysts, phosphine ligands, etc.) will require some processing in order to recover or, indeed, will form part of the waste output. Accordingly, high-ranking AE and RME reactions can be misinterpreted as being remarkably efficient when essential additives are omitted and/or the potential for recyclability is overestimated.

As briefly discussed above, the stoichiometry of reagents is significant and can lead to misinterpretation of AE and RME outputs between reaction classes due to either omission of stoichiometry or the reliance of the calculation on mass units. For example, Scheme 3 shows a typical example of a ketone reduction using $NaBH_4$ (Table 2, entry 13b).

Here, AE is 92%, restricted E-Factor is relatively good at 1.5 (198 with inclusion of solvent), and RME is moderate at 40%. However, the AE value is misleading as the mass differential is low, and the E-Factor/RME values, while modest, are also misleading because the molecular weight of $NaBH_4$ is very low. Even though the AE of this reaction is the highest of the reduction reactions surveyed (Table 2, entries 13a–c) and the restricted E-Factor/RME of reaction 13b is in the middle of the observed range, the Mol. E calculation (and restricted E-Factor with inclusion of solvent) suggests that this reaction is actually the least efficient due to the stoichiometry of the hydride reducing agent.

Solvent represents the largest fraction of the total material used in pharmaceutical manufacture and is one of the principal contributors to the waste output of synthetic operations.[79] While solvent is typically essential for the majority of chemical processes, considerable efforts continue to be made to lower the impact of solvents through reduction, replacement, and/or recycling.[1−4,79−84] As such, we believe that an efficiency index should take this primary contributor into account in order to realistically assess a particular reaction or process. Of the three main established metrics discussed (AE, E-Factor, and RME), E-Factor is unique in its consideration of the impact of solvent. In this respect, an analysis by mass can again be misleading as the molecular weight and density of solvents varies widely. As an example, electrophilic aromatic substitution is a very useful and routine method for the synthesis of functionalized aromatic frameworks. However, as with many of the staples of organic chemistry, the concentration of such reactions can vary widely. Scheme 4 illustrates two examples from Table 2 (entries 7b and 7c) that involve the Friedel–Crafts acylation of electron-rich aromatics. These reactions proceed under similar conditions (chlorinated solvent, promotion by $AlCl_3$, heated) and have approximately the same AE (about 90%), restricted E-Factor (without solvent, about 2), and RME (about 30%). Accordingly, to discriminate them from each other, one may be tempted to rely on the yield of each process. Such an analysis suggests that reaction 7b would be the more efficient (89% vs 53% yield). However, comparison of the solvent included restricted E-Factor and Mol. E values suggests otherwise; Reaction 7b was performed at 0.25 M, while reaction 7c was performed at 2.15 M. Accordingly, the solvent included E-Factor and Mol. E values of reaction 7c are approximately double that of reaction 7b. Once more, the issue

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of solvent density arises in that the E-Factor calculation suggests that reaction 7c is more efficient than reaction 7b by a factor of 1.9, while Mol. E suggests reaction 7c is more efficient by a factor of 2.6.

Analysis by Mol. E therefore allows the effect of solvent to be gauged comprehensively and across different reaction types while alleviating any problems that may be associated with molecular weight/density inconsistencies. This may encourage practitioners to consider if a high dilution is actually necessary or if a lower solvent volume would be practicable.

CONCLUSIONS

In summary, molar efficiency has been introduced as a new metric for calculation of reaction efficiency particularly within a drug discovery setting. Calculations from molar units enable inclusion of all reaction inputs and are helpful to avoid any issues of misinterpretation due to inconsistencies of molecular properties. On the basis of its holistic nature, we believe Mol. E is a useful yardstick for reaction evaluation, especially cross-evaluation of different reaction types. Consequently, we believe that molar efficiency may enable discovery chemists to assay and compare the types of reactions being employed in medicinal chemistry programs and encourage a dialogue to increase the uptake of more efficient and sustainable transformations.

ASSOCIATED CONTENT

Supporting Information

Reaction schemes set for efficiency calculations and associated data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

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ABBREVIATIONS

AE, atom economy; LG, leaving group; Mol. E, molar efficiency; PG, protecting group; Phth, phthalimide; PMI, process mass intensity; RME, reaction mass efficiency; SEM, trimethylsilylethoxymethyl; Ts, *p*-toluenesulfonyl.

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