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Mass Efficiency of Alkene Syntheses with Tri- and Tetrasubstituted Double Bonds

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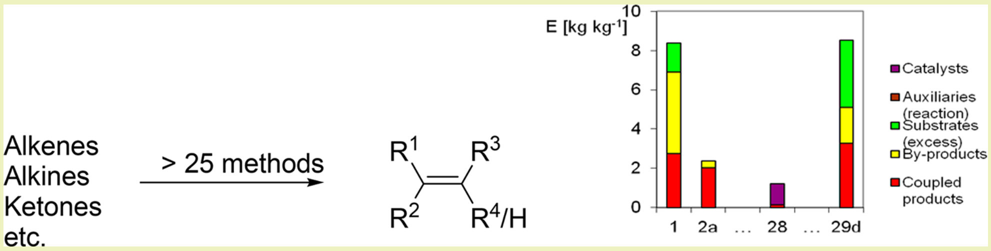
Supporting Information



ABSTRACT: Environmental factors and process mass intensity were determined and evaluated for more than 30 standard procedures for the synthesis of alkenes with tri- and tetrasubstituted double bonds. They contain some of the most commonly used reaction types for the synthesis of alkenes, e.g., Peterson, Shapiro, Heck, Suzuki, and Negishi. Four kinds of syntheses of geminal dihalides were also considered. The highest efficiency is found when employing the olefin metathesis reaction followed by other modern catalytic processes, and the lowest efficiency is found with the Julia–Lythgoe process. Several types of McMurry coupling reactions show that the efficiency is dependent on the variant of this type of reaction. These metrics point out weaknesses as well as optimization potentials and show which performances can be expected. This could provide an orientation when mass efficiency aspects are relevant during the synthesis planning of alkenes with tri- and tetrasubstituted double bonds.

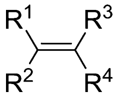
KEYWORDS: *Alkenes, Environmental factor, EATOS, Process mass intensity, Waste prevention*

INTRODUCTION

The regio- and stereoselective synthesis of alkenes with tri- and tetrasubstituted double bonds is a central topic in current organic chemistry.[1] The importance of this field is highlighted by the edition of a volume about this topic in the series "Science of Synthesis",[2] edited by the publisher Thieme, Stuttgart. 1,2-Elimination reactions of alcohols and esters (Chapter 47.1.4.5 of ref 2) were the first ones used for the synthesis of alkenes during the beginning of organic chemistry and are still applied, meaning the syn-elimination reactions in drug synthesis.[3] Within the last five decades, new and more efficient methods have been developed.[4−6] The synthesis of alkenes with tri- and tetrasubstituted double bonds was greatly improved with the development of catalytic procedures.[7−10]

The design of an alkene affects four substituents (R^1–R^4, Scheme 1), whereby these substituents can be identical, defining a kind of symmetry when, e.g., $R^1 = R^2 = R^3 = R^4$ or $R^1 = R^2 = R^3$ or $R^1 = R^2$ or $R^1 = R^3$. Within these groups, R can also be part of a ring system.

Scheme 1. Formal Presentation of the Structure of Different Types of Alkenes with Groups R^1–R^4[a]



[a]In this examination, most of these are alkyl or aryl groups, and some are, for example, a COOR group. One rest R could be hydrogen.

Alkenes with a tri- and tetrasubstituted double bond with a variety of alkyl- and/or aryl groups are of interest for two main reasons. First, the alkenes are found as natural products and are considered to be pharmaceutically important products, for example, Tamoxifen and Radjadone. Syntheses of these alkenes are driven by the demand for preparing new biologically active products, see for example a comprehensive review by Flynn and Ogilvie.[11] Second, the alkenes are prepared and used as model compounds for studies in physical organic chemistry.[12]

Yield and control of selectivity remain at the center of optimization efforts when developing synthetic protocols. However, the overall performance is also relevant (e.g., number of steps, amount of substances and their properties, such as toxicity or odor). In this regard, several alternative bromination methodologies were examined,[13] intending to replace neat bromine because of its hazards. Remarkably, many of the variants considered apply hazardous substances and produce large amounts of waste. This could be called "green chemistry

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Table 1. Synthesis Examples of Selected Methods for the Synthesis of Alkenes with Tri- and Tetrasubstituted Double Bonds[a]

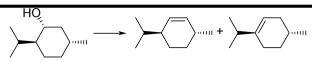
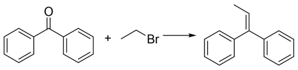
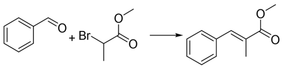
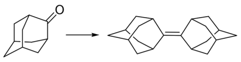
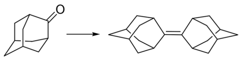
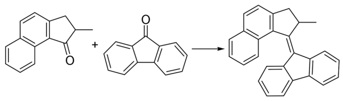
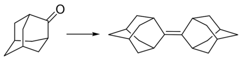
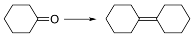
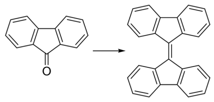
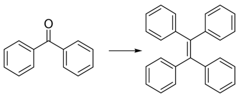
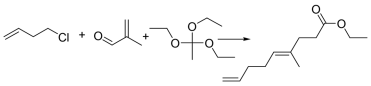
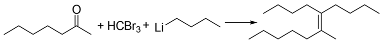
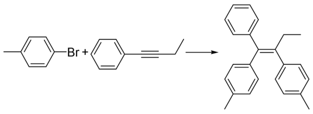
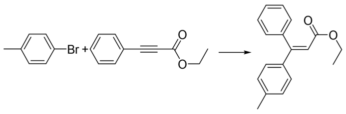
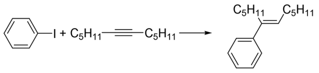
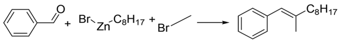
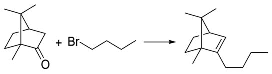
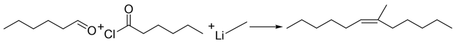
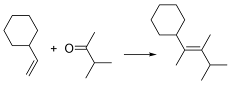
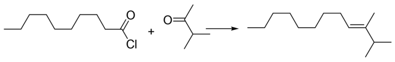
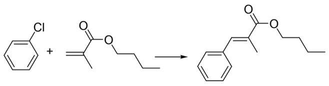
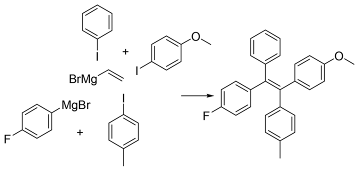
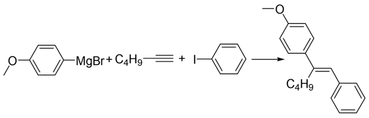
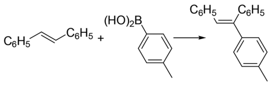
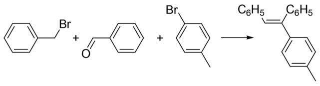
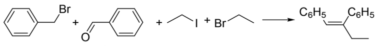
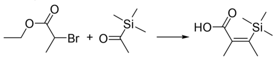
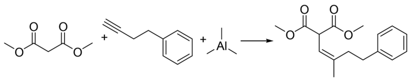
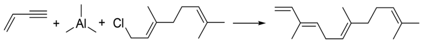
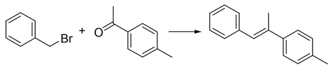
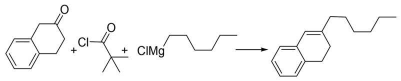
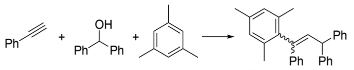
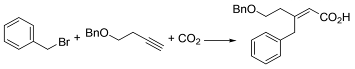
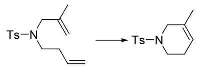
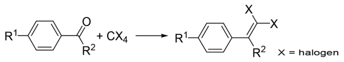
No.	Method	Literature	Steps	Constructive hydrocarbon reagents and the product of the synthesis sequence
1	ß-Elimination (Tschugaeff)	19	2	
2a	Wittig Reaction	20	3	
2b	Wittig Reaction (catalytic)	21	2	
3	Carbene Dimerisation	22	2	
4a	Barton-Kellogg's extrusion process	23	2	
4b	Barton-Kellogg's extrusion process (asymmetric variant)	24	5	
5a-d	McMurry Coupling [b]	25-28	2	
5e	McMurry Coupling	29	3	
5f	McMurry Coupling	30	1	
5g	McMurry Coupling	31	1	
6	Claisen rearrangement	32	2	
7	Alkylation – elimination process	33 34	3	
8	Suzuki-Miyaura (Zhou, Larock)	35	3	
9	Hydroarylation	36	3	
10	Arylzincation	37	2	
11	Method of Coupling by Negishi	38	4	
12	Shapiro	39	3	
13	Peterson	40	3	
14	Julia-Lythgoe	41	7	
15	Thiolester conversion	42	3	
16	Heck	43	1	
17	Heck	44	5	

Table 1. continued

No.	Method	Literature	Steps	Constructive hydrocarbon reagents and the product of the synthesis sequence
18	Arylmagnesiation of Aryl(alkyl)acetylenes	45	3	
19a	Coupling of Vinylbromides (Suzuki)	46,47	3	
19b,c	Coupling of Vinylbromides (Suzuki)	46-49	7	
20	Coupling of Vinylbromides (Negishi)	46,47	7	
21a,b	Ynolate conversion (Shindo)	50	a: 6 b: 3	
22	Opening of cyclopropenes (Wang)	9 (51-54)	4	
23	Allylation of Alkenylalanes	55	2	
24	Organozinc reagents and carbonyl compounds (Wang)	56	2	
25	Cross-coupling of alkenyl-carboxylates with Grignard reagents	57	2	
26	Three component reaction (Li)	58	1	
27a,b	Alkylative or Arylative Carboxylation of Alkynes	59,60	a: 2 b: 6	
28	Olefin Metathesis	61	1	
29a-d	Geminal dihalides	62-65	a: 2 b: 1 c: 3 d: 1	

[a] Method specific auxiliary materials are shown in Table S1. For a full presentation of all synthetic steps and reaction details, see Tables S7 and S8. [b] Ref 25 is according to ref 66.

paradox".[14] Costs are important as well and were determined for substances necessary for alkene bromination.

In a similar manner, we would like to examine the synthesis of alkenes with tri- and tetrasubstituted double bonds because environmental, health, and safety aspects are crucial for further scale-up procedures and for the design of a technical production process.[3]

The aim is to obtain an overview of the resource efficiency of some procedures (Table 1). Our study provides a comparison of the respective protocols delivered by the original works with regard to green and sustainable chemistry when performance metrics are not presented. For example, if a chemist is interested whether the Wittig reaction is green compared to alternative procedures, he can obtain information on the basis of a range of mass metrics.

Synthesis protocols in the literature, like those resulting in alkenes with tri- and tetrasubstituted double bonds, usually treat different products and, additionally, fall back on substrates showing different degrees of complexity. In this case, it seems reasonable to retrace the synthesis sequence back to starting materials showing a similar refinement. Therefore, we will approach a recommendation made by the German Federal Environmental Agency (Umweltbundesamt) to a certain extent. This authority[15] proposes to examine the entire production process, which includes looking at all upstream production operations for starting and auxiliary materials and all downstream processing operations for alternatives or new pathways of synthesis. Studies such as these will contribute[16,17] to greater sustainability. For a quantitative assessment, one should use metrics.[18]

In an initial but rather rough approach, compounds such as ketones, aldehydes, halogenated hydrocarbons, "simple" alkenes, and alkynes could be considered as equivalent starting materials. In Table 1, a range of alkene syntheses was collected beginning with these functional groups.

■ METHODOLOGY

The synthetic protocols of alkene synthesis are multivariant with a large variety of reactants and substances. Therefore, if one does not consider a distinctive target molecule but rather many protocols described in the literature, substance properties are not really concept specific and raw material costs are not informative. Thus, we will limit ourselves to the resource efficiency by determining the environmental factor E[67] and process mass intensity PMI, whereas according to the numeric value, the latter is nearly the same.

$$E = \frac{m_{\text{waste}}}{m_{\text{product}}} = \frac{m_{\text{input}} - m_{\text{product}}}{m_{\text{product}}} \tag{1}$$

$$\text{PMI} = \frac{m_{\text{input}}}{m_{\text{product}}} = E + 1$$

$$\left(= \frac{m_{\text{input}} - m_{\text{product}}}{m_{\text{product}}} + \frac{m_{\text{product}}}{m_{\text{product}}} = \frac{m_{\text{input}} - m_{\text{product}} + m_{\text{product}}}{m_{\text{product}}} = \frac{m_{\text{input}}}{m_{\text{product}}} = \text{PMI} \right) \tag{2}$$

where variable "m" refers to mass.

These metrics show a lot more than one expects. High solvent demand, for example, means energy-intensive recycling, which correspondingly affects global warming and other impact categories of a life cycle assessment (LCA). As a consequence, mass balance and LCA deliver the same result for the synthesis of a pharmaceutical intermediate (see pages 203−204 in ref 68 or 69) and a photocatalytic[70] reaction. Another LCA examination[71] supports that mass-related metrics such as the process mass intensity (PMI) seem to be very reliable. On the other hand, a less meaningful metric is the atom economy AE.

$$\text{AE} = \frac{\nu_{\text{product}} \cdot \text{MW}_{\text{product}}}{\nu_{\text{A}} \cdot \text{MW}_{\text{A}} + \nu_{\text{B}} \cdot \text{MW}_{\text{B}} + \ldots} \tag{3}$$

where "MW" corresponds to molecular weight with appropriate stoichiometric coefficients "ν" and with reagents A, B, and so forth delivering the product.

To facilitate such calculations, we developed a software tool 15 years ago called Environmental Assessment Tool for Organic Syntheses (EATOS),[72] which we apply for reasons of convenience during our studies. This tool, which uses the term mass intensity S^{-1} for PMI, not only performs calculations of the E-factor and the PMI for single syntheses and linear and convergent synthesis sequences but also considers raw material costs and type/quality of waste. This java application is available at no cost on the Internet[73] and has been applied by other scientific groups. Recently, two additional Excel-based tools have been made available with which PMIs of linear as well as convergent synthesis sequences can be determined.[74,75] In a current study, up to seven algorhithms have been evaluated,[76,77] and EATOS was recommended[76] by the author. A further examination deals with qualitative aspects such as the environmental and hazard impact, which can be considered with these seven methods.[78]

RESULTS

The overall yield of most procedures is moderate to good. For an idea of the overall stoichiometry, the atom economy[79,80] of the synthesis protocols is also presented (Table 2).

Stereochemical Aspects. We would like to point out a special section in March's textbook[1] called "Regiochemistry and Stereochemistry of the Double Bond". In principle, six isomers exist for alkenes with four different R groups. Given an alkene with one rest in the first instance, there are three possibilities to allocate one of the remaining three rests to the second position. The third position can be taken by two remaining rests, which means there are two possibilities. The last position is reserved for the fourth rest. In total, the number of theoretical possibilities is 3 × 2 × 1 = 6.

However, the choice of substrate normally only allows the formation of less than six isomers. Starting with a ketone R-CO-R, for example, means that two rests (R^1 and R^2 or, when symmetric, two R^1) will be bound to one of the carbon atoms of the double bond. This means that one of them cannot be placed at the other, and thus, four isomers are principally not possible: only *Z* and *E* isomers remain. Table 3 can serve as an orientation regarding a synthetic problem considered. For example, if one wants to synthesize the type $R^1R^2{=}\,R^1R^3/H$, the protocols of entries 20, 19b, 19c, 8, 19a, and 10 can be taken into account. Of course, other protocols are conceivable as well.

Mass Metrics. *Presentation of Data.* A presentation as shown in Figure 1 conveys a better impression of the environmental factor subdivided into coupled products, substrate excess, and so forth than the numbers in Table 2. As can be seen, specific environmental factors *E* differ significantly. However, solvents and aqueous solutions used during the performance of the reaction and workup procedure are not indicated in the column diagram. Their optimized application is generally not the focus of a scientific publication. This is not even common in high quality publications such as *Organic Syntheses*, where the protocols are tested. Syntheses from this journal have been considered in entries 5d, 6, 9, 12, 15, 16, 21, 23, 25, and 29a. To be complete and to give an idea of the solvent and washing method, we note the amounts within the table below the diagram in Figure 1. Thus, the diagram simply shows the amounts of coupled products, byproducts, catalysts, and so forth (see legend). The term "byproducts" means a substance resulting from competing reactions, i.e., they are also called side products. Coupled products are formed together with the product according to the stoichiometric chemical equation, and they are also called byproducts. Additionally, the amount of solvent utilization is often not noted at all in the literature. As a consequence, these masses are missing altogether in the first row of the table of Figure 1. Thus, the number of solvent applications without data is presented in the third row. As solvents significantly increase energy demand and generation of emissions, they should at least be considered in a qualitative or semiquantitative manner. Environment, health, and safety (EHS) concerns associated with the use of solvents can be addressed using strategies for solvent selection.[83−87] Solvent application is presented in detail in Table S9. To demonstrate that the differences in the molecular weights do not have a significant influence on the results, we present the relation of waste to one mol as unit instead of one kilogram of product in Figure S1b. The comparison of Figure 1 and Figure S1b essentially reveals only slight differences. Merely entries 4b, 5g, 8, 17, and perhaps 27b show a relatively high waste column. Thus, Figure 1 is appropriate to facilitate a comparison of all synthesis sequences.

Influence of Preceding Steps/Refinement of Substrate. Entries 19a and 19b exemplarily illustrate the effect when earlier steps in the synthesis sequence have been considered: whereas entry 19a begins with an alkene with a disubstituted double bond, entry 19b considers its synthesis using the Wittig type. Although the Heck protocol in entry 16 originates from a higher refined alkene and ends with three substituents, the variant in entry 17 starts with a very simple alkene to which four substituents have to be added. Consequently, in each case, the latter shows a higher material demand and waste production

Table 2. Summary of Metrics of Alkene Syntheses According to Table 1 and Stereochemical Information

no.	yield[a] [%]	AE[a] [%]	E-factor[b]	selectivity	ratio of Isomers
1	36	35	8	high, syn elimination[f]	3:1 (1-menthene/2-menthene)
2a	86	34[c]	2[c]	high, kinetic control of intermediate phosphetane[g]	~95:5; other isomer is formed by thermodynamic control by adding Li salts) or by crown ether catalysis[g]
2b	77	34.5[c]	4[c]	high, kinetic control from intermediate[g]	~95:5; syn-products are preferred
3	72	28	15	not known, side products	not known[h]
4a	65	23	11	low	not known
4b	32	26	17	low	not known
5a−g	76−97	12−57	3−27	medium to high, depends on R^1 and R^2 and variant[i]	some E/Z selectivity; e.g., 100:1 with *tert*-Bu and CH_3
6	60.7	51.2	6	high	E-isomer
7	62	24	12	high	mainly one isomer (syn)
8	80	33.2	11	medium to high[j]	10:1−5:1 syn/anti products
9	77[e]	44.1	4		excellent syn selectivity
10	82	49.3	5	medium to high	syn over anti addition isomers
11	67	30	8	high	one isomer[k]
12	38.7	25.6	9.7	high[d]	one isomer[d]
13	31.6	11.1	33.9	high	98:2 Z/E (basic elimination: 5:95)
14	22	11	49	high	one isomer[41]
15	67.5	28.7	7.6	medium to high (byproducts identified)	E:Z = 27:1
16	96	48.5	1.4	high	E:Z > 20:1
17	29.4	20.4	18	medium to high	one isomer[l]
18	91	43.2	7	high (<3% regioisomer)	mainly syn-addition products[45]
19a	68	50	6	high, one isomer is isolated	syn-addition products[47]
19b	42	22	13	high, one isomer preferred	syn-addition products[48]
19c	50	22	13	high, one isomer preferred	syn-addition products[m]
20	47	21	27	high, one isomer preferred	syn-addition products[k]
21	62	16	14−15	high[50]	one isomer[50]
22	42	45	6	high, one isomer preferred	one isomer[51−54]
23	83	55.3	3.5	high for γ,γ-disubstituted allyls	>98%
24	76	56	3	high, one isomer preferred	
25	94	45.4	2.5	high	acyclic ketone: E/Z = 2:1
26	82	96	1	weak, mixtures of isomers	structures not known[58]
27	79	64	4−9	high	structure not known
28	99	90	1	strong, medium partly possible	some isomers are favored due to thermodynamic stability[n]
29a−d	74−90	23−51	5−9		

[a] Yield and atom economy[79,80] in chosen examples (for details, see Tables S7 and S8). [b] Rounded values conditioned according to the columns in Figure 1. However, information on solvent and auxiliary amounts (see table of Figure 1) are not integrated here! The underlying data are given in Tables S3 and S4. [c] E-factor and atom economies of the Wittig vinylation can be found in the literature.[82] [d] Other substrates show mixtures of isomers. [e] Yield of other reactions is up to 94%. [f] Ref 1, pp 1288−1289. [g] Ref 1, pp 1165−1173; see also ref 81. [h] Ref 1, p 1255. [i] Ref 1, p 1559. [j] Ref 1, p 1771. [k] Ref 1, p 1524. [l] Ref 1, pp 1683, 1692, and 1763−1768. [m] Ref 1, p 1560. [n] Ref 1, p 1417−1423.

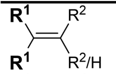
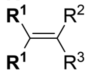
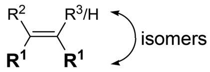
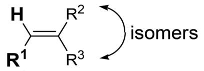
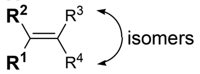
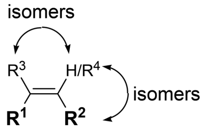
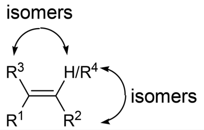
(Figure 1 and Table 2). Of course, the result depends upon which preceding step will be considered (compare entry 19b with 19c regarding different bromination procedures). A look at the auxiliary material is also interesting. In entry 27, diazabicycloundecen (DBU) is used in large amounts. Its synthesis can be considered for evaluation as well (entry 27b).

All Procedures at a Glance. According to the environmental factor, the olefin metathesis reaction (entry 28, Figure 1), a three component reaction (entry 26), and one of two Heck reactions (entry 16) are the most efficient methods of all alkene syntheses with less than ~1.4 kg of waste per kg of product. There is no need for the high solvent and sewage amount indicated in Figure 1. The Julia−Lythgoe method, entry 14, is the least mass-efficient method. Syntheses in entries 5e, 5g, 13, and 20 (McMurry variants, Peterson and Negishi reaction) also have a high generation of waste, whereby in 5g, the auxiliary material will probably be recyclable to a very high degree. This auxiliary material is SiO_2, which will perform the ball milling process more efficiently. A Barton−Kellogg's extrusion process (entry 4b) and a Heck-variant (entry 17) are slightly more mass efficient but still produce at least 17 kg of waste per kg of product. Beyond that, six chromatographic isolation procedures are used in this Heck variant. The other methods are in the range of approximately 15.4 to 1.6 kg kg^{-1} in descending sequence:

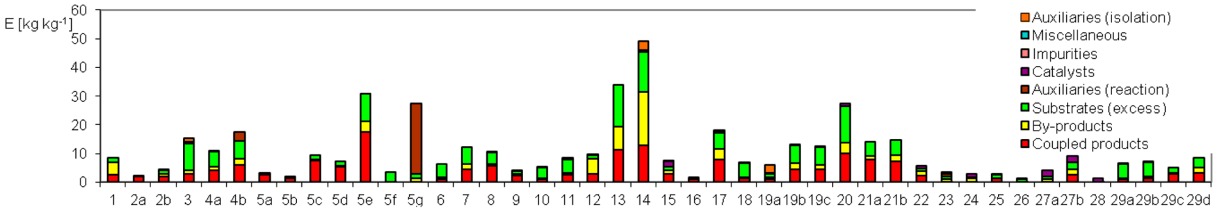
15.4−10 kg kg^{-1}:	3, 21b, 21a, 19b, 19c, 7, 8, 4a
10−5 kg kg^{-1}:	12, 5c, 27b, 29d, 11, 1, 15, 5d, 18, 29b, 6, 29a, 19a, 22, 10, 29c
5−1.6 kg kg^{-1}:	2b, 27a, 9, 23, 5f, 5a, 24, (5g in case of SiO_2 recycling), 25, 2a, 5b

It should be emphasized that a side view regarding the solvents and some other aspects are necessary (see table of Figure 1), e.g., the effort expended in entries 22 and 28 (see solvent: 1770 and 846 L) is striking. Because of the washing procedures, inorganic substances have to be applied and disposed; see "salts, acids, and bases" in Figure 1. This means that the actual PMI and E-factor is higher than the stated value depending on

Table 3. Sorting of Alkene Syntheses According to the Structure Given by One of the Building Blocks

Product / Type [a] Bold rests originate from one of the substrates	Number of possible isomers	Entries of this article with declining E factor according to Table 2 and Figure 1 [g] decreasing E-factor →
	1	5e, 5g, 3, 4a; 5c, 5d, 2b, 5f, 5a, (5g) , 2a, 5b
	1	4b, 7
	2	20, 19b, 19c, 8, 19a, 10
	2	27b[d], 11, 22[b], 27a[d], 24, 26[c] (in principle, some of the methods of the first row are applicable as well)
	2	14, 13, 21b[f], 21a[f], 12, 15, 16, 28[e], (in principle, some of the methods of the first row are applicable as well)
	4	12, 6, 9, 25[h]
	4	18, 23

[a] The double arrow marks those rests that could have the opposite postion resulting in the formation of isomers. [b] R^1 has two electron-withdrawing groups (EWG). [c] R^1 is a carbon atom with one or two aromatic substituents, and both R^2 and R^3 are aromatic. [d] R^1 is a COOH-group. [e] Concrete example shows R^1 and R^4 to be a ring and R^2 to be a hydrogen atom. [f] R^3 or R^4 is a COOH-group. [g] Entry 1 was not allocated. [h] R^1 and R^2 are rings in most examples.



	1	2a	2b	3	4a	4b	5a	5b	5c	5d	5e	5f	5g	6	7	8	9	10	11	12	13
Org. solvents [kg kg^{-1}] [a]	13	17	13	163	226	92	51		160	409	551	125	25	15	408	1094	25	15	162	76	415
Different solvents [-]	3	3	4	5	5	7	3	1	2	3	4	4	1	2	4	4	4	4	6	5	4
Solvent utilizations without mass data [-] [b]	1		2	1	3	4	1	1	1		2	2			2	1		1	1	0	0
Chromatography			1		1	3						1			1	1	1	1	1	0	3
Sewage/water [kg kg^{-1}]		8		15	125	82	125				51			9		241	2	26	194	209	220
Salts, acids & bases [kg kg^{-1}]						19.4	2.3			4.8	1			1.3		87.4		7.6	7.3		49.8

	14	15	16	17	18	19a	19b	19c	20	21a	21b	22	23	24	25	26	27a	27b	28	29a	29b	29c	29d
Org. solvents [kg kg^{-1}] [a]	1729	44	27	253	25	138	155	150	90	169	169	1770	18	15	224	4	70	103	846	41	164		20
Different solvents [-]	7	4	3	8	5	3	6	7	5	4	4	6	4	4	4	2	5	8	2	5	3	2	2
Solvent utilizations without mass data [-] [b]	1	1	2	15	4	1	1	1	1			2	2	2	0	1	4	4	2	.	1	4	1
Chromatography	1	1	1	6	2				2			2	1	1	2	1	1	1	1	1	1		1
Sewage/water [kg kg^{-1}]	1920	73	27	92		78	87	95	25	92	92	463	10	5	36				4018	58	228		
Salts, acids & bases [kg kg^{-1}]	283.9	8.6	4	8.6		11.8	14.6	14.6	3.8	10.8	10.1	42.2		1.4	5.7			0		5.9	8.5		

[a] Only those solvent amounts are indicated here, which have been described in literature. [b] Number of solvent applications for which no information about amounts are given. Repeated application of the same solvent is possible.

Figure 1. Environmental factor related to 1 kg of product of some alkene syntheses (Tables 1 and 2) determined[72] according to the literature. Its relation to 1 mol can be found in Figure S1b. The underlying data are given in Tables S3 and S4. Quantities of solvents, salts, acids, and bases are not shown in the columns but as numbers in the table for the neat substance without water. Auxiliary materials such as salts (e.g., brine), acids, and bases (e.g., sodium hydroxide) are also listed separately in detail (see Table S5). Reaction equations and conditions are shown in Tables S7 and S8. The solvent applications are given in Table S9, and the number of chromatographic isolation procedures is indicated here. Assumptions made are presented in Table S10. Workup procedures, which were not described quantitatively in literature and had to be omitted, are listed in Table S11.

how much optimization potential can be assumed for the literature protocols. Although we feature only one representative of a respective reaction type, the results can convey an idea about the potential resource demand and waste production and thus provide assistance for choosing the most efficient synthesis.

Comparing the atom economies of all reactions (Table 2), the Wittig reaction, which has often been used as a poor example in green chemistry discussions, is not really prominent, there are many other syntheses with an atom economy below 40%. Obviously, the synthetic challenge of the alkene preparation does not present easy answers. Nevertheless, there are some procedures that are very efficient in atom economy (entries 26 and 28). Furthermore, relatively high atom economies of the organo-zinc preparations (entries 10, 24, and 27) and further protocols (6, 16, 19a, and 23) are noteworthy. Interestingly, the mass efficiency basically correlates with the atom economy for these protocols as well as the most and least efficient protocols (entries 28, 26, 13, and 14). However, normally such a correlation cannot be observed,[88] possibly because solvents and a range of auxiliary materials have not been integrated in the environmental factor presented in Table 2.

Variants of One Reaction Type. Variants of a given reaction type can have a significant effect on the environmental factor. This is shown for the six types of McMurry coupling reactions, entries 5a–g. Entries 5a and 5b, which use $TiCl_4$ and zinc reagents, are the best examples, and entry 5e is the worst. When silica SiO_2 is reused, entry 5g is resource efficient as well. In contrast to this example, the environmental factors of geminal dihalogenide syntheses (entries 29a–d) are similar. They play an important role[89] for alkene syntheses (see, for example, entry 11).

Changing a reaction step (here, a bromination reaction) within a synthesis sequence (Table S7, step 3 in entries 19b and 19c) always has somewhat of an impact on the overall environmental factor (Figure 1, entries 19b and 19c). The conventional bromination, using molecular bromine, produces slightly more waste than the hydrogen bromide/peroxide system. The catalytic Wittig-type reaction (entry 2b), which uses a silicon[90] instead of a phosphorus compound, does not show an improvement compared to that of the classical Wittig reaction (entry 2a). The question is which coupled product can be recycled in a more environmentally friendly way. Attempts are regularly reported in the literature.[90,91] There does exist a commercial procedure for the classical variant of the Wittig reaction with triphenylphosphonium salts.[92] The authors of the new method[90] using a silicon compound argue for presenting an atom-efficient catalytic procedure but deliver no metrics. Actually, the environmental factor is worse than the classical variant. Against this background, J. Andraos demands to back up claims of "greenness" or synthetic efficiency with some kind of metrics analysis.[93]

Whereas Figure 1 shows the transformation products (coupled and byproducts) and excess of substrates, catalysts, and so forth, the substrate demand is specifically indicated in Figure 2. In this regard, Figure 2 shows the metric "(process) mass intensity"[94] ($S^{-1,72}$) although shortened to only reactants because solvents and so forth are already given in Figure 1. Therefore, Figure 2 is a reciprocal of the "reaction mass efficiency (RME)",[94] i.e., 1/RME. Additionally, showing the substrate masses per reaction step conveys how many steps were necessary to synthesize the alkene. A darker top of the column means more reaction steps were required (for details, see Table S7). The number of reaction steps of side chains is not indicated here, yet shown are the masses of their substrates. Entries 14, 13, 5e, and 20 show the highest substrate demand.

■ DISCUSSION

Comparison of Various Alkene Syntheses. Mass efficiency is one of many important aspects in synthesis design. It is more crucial, though, whether a synthesis protocol tolerates existing functional groups or allows for easy purification of the desired product. Aside from this, there are more relevant aspects. For example, a mass-efficient three-component reaction (entry 26) includes an electrophilic aromatic substitution reaction with an arene. As arenes have several positions for an attack, the choice of substrate is somewhat limited to keep the number of isomers small. However, corresponding alkenes are synthesized very efficiently with this method. One of the most frequently applied methods is the metathesis considering appropriate[95] catalysts requiring two alkenes. The appropriate substrates are either readily available or they will possibly have to be synthesized by other methods. In that case, several steps have to be considered. For example, in the reaction by Suzuki (entry 19a), we prefixed the Wittig reaction (entries 19b–d, Table S7). Of course, the result is quite different then because the number of reaction steps in entries 19b–d is higher than in entry 19a. Against this background, it is possible to assess the application of alkynes. The arylmagnesiation (entry 18) considers preparation of the necessary alkyne (or of the ynolate in a reaction in entry 21). On the contrary, other methods are presented, already beginning with a specific alkyne (entries 8, 10, 22, 26, and 27), which can be prepared for example by the Sonogashira[96] reaction. Therefore, statements such as "organo-zinc[97−99] preparations (e.g., entries 10, 24, and 27) seem to be resource efficient" have to be made and understood with a lot of care. A certain E-factor for the synthesis of reactants has to be kept in mind. This is also true for other substances used (see, e.g., diazabicycloundecen (DBU) in entry 27ab) and even for those for which small amounts are used. Some of the reactions highlighted in this paper rely on very rare platinum group/precious metals that have enormous environmental impacts associated with their mining, purification, and transformation into catalysts, or the catalysts themselves have complex syntheses with low mass efficiency. This is another green chemistry paradox: catalysis is central to green chemistry, but modern synthetic organic chemistry is sometimes carried out using substances with an unsustainable (potentially hidden) background. Its (partial) integration creates more clarity. To give an example, mass efficiency and raw material costs were compared for the (a) biocatalytic and (b) chemical catalytic enantioselective epoxidation of styrene.[68] In this case, it is of interest whether or not the production of bacteria and the synthesis of the Jacobsen catalyst was taken into account. Additionally, the current examination only takes a look at the synthesis of the product, which indeed normally delivers a mixture of isomers. The results for stereoselectivity are summarized in Table 2 and Table S2. Mixtures of isomers can be separated either by repeated crystallizations or by separation using preparative

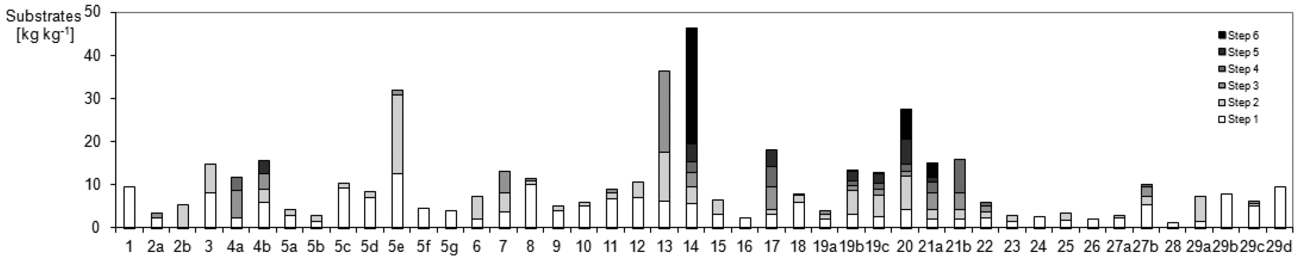


Figure 2. Substrate amounts for some alkene syntheses (Table 2). All other materials are shown in Figure 1. The underlying data are given in Table S6.

chromatography. The isolation of single isomers is not always described in the literature; therefore, it could not be considered in this study. Thus, the kilogram of product to which the mass balance relates consists of the isomeric mixture. This means that a synthetic plan (Figure 1) that appears to be more efficient than another could turn out to be worse when product purity is not sufficient and an isolation procedure has to follow. Therefore, a protocol such as the ynolate conversion (entry 21) producing a Z:E ratio of 99:1 could be more sensible than an alleged resource efficient alternative with worse selectivity. For example, the β-alkyl-α,β-unsaturated ester synthesis[100] via alkylcuprates is accompanied by the formation of a byproduct that could not be separated by flash chromatography.

Alkenes are used as starting materials in four of the considered syntheses: the Claisen rearrangement (entry 6), the Julia−Lythgoe reaction (entry 14), the new coupling methodologies (by Heck, Suzuki, and Negishi, entries 16, 17, and 19), and the metathesis (entry 28). The second, though showing moderate to excellent E/Z selectivity, unfortunately results in a high waste production (Figure 1). The Heck, Suzuki, and Negishi procedures we considered show even better selectivities but are limited to aryl substituents. According to the mass efficiencies, the alkene metathesis (entry 28) seems to be the first choice as a general procedure. However, sometimes there are other sensitive double bonds in the substrates. Sometimes, the substrate is available with a keto or aldehyde group for economic reasons. In that case, the McMurry (e.g., entries 5a and 5b), Wittig (entries 2a and 2b), possibly Peterson (entry 13), or modified Shapiro reactions (entry 12) or reaction entry 25 could be recommended.

Carbonyl compounds as starting material are proper, especially for the McMurry (e.g., entries 5b and 5a), Claisen rearrangement (entry 6), or Wittig (entries 2a and 2b) reaction as well as zinc (entry 24, 27) or Grignard (entry 25) applications, which could be recommended. However, selectivity is not always perfect. The Wittig reaction is quite general. The McMurry reaction is known for symmetric products such as the carbene dimerization (entry 3), but it is not limited to these. There are cross coupling reactions[101] and intramolecular couplings.[102]

Using alkynes as starting material seems to be promising for the synthesis of partly symmetric (entries 8, 10) to asymmetric (entries 9, 18, 22, 23, 26, and 27) (especially aryl-) alkenes regarding both waste minimization and selectivity (except, for a part, entry 18). The number of reaction steps is relatively low (Figure 2). In case there is a higher degree of symmetry, ketones could be chosen in the McMurry (entry 5b) and Wittig (entry 2) reactions. Carbonyl compounds are also a synthon in the methodologies of organozinc reagents (entry 24), geminal dihalides (entry 11), and some others (entries 12 and 13), which show high selectivity for more asymmetric targets.

Alternative Procedures. Geminal dihalides were exemplarily examined (entries 29a−d) to demonstrate some of the considerations that play a role in the decision process. Assuming a superior recyclability for the substrates in entries 29a and 29b compared to the coupled products in entries 29c and 29d, the former seem to be more efficient. Although the yield in entry 29a is better than that of entry 29b, the respective solvent application shows an opposite efficiency (Table S9). The methylene chloride amount dominating the solvent utilization in entry 29b can easily be reduced while there are five different solvents in entry 29a, which are also more dangerous regarding safety issues. Thus, a clear position is not possible. A similar finding is delivered by alternative bromination reactions in entries 19b and 19c (Figure 1). In this case, the difference is so marginal that other points might become more relevant, such as (raw material) costs or safety/health issues. However, it has to be clear that alternative procedures can also produce great deviations, which is illustrated by a look at the six syntheses of adamantylideneadamantane (entries 3, 4a, and 5a−d). This can also be seen in both Heck reactions (entries 16 and 17) differing by the degree of refinement concerning the starting alkene.

Stereocontrol of the elimination reaction is only possible in E-2-type eliminations. These eliminations follow an antiperiplanar reaction path. Generation of byproducts is often inevitable, and isolating the product from isomeric products is difficult. Additionally, the application of carbon disulfide and handling of xanthates (entry 1) is a chemistry not recommended due to its hazards. Arylmagnesiation (entry 19) is limited to 2-fold arylsubstituted alkenes. Arylzincation (entry 10) admittedly also takes monoarylated alkenes into account, however, asymmetric aliphatic alkynes deliver no or moderate yield with an unsatisfying E:Z ratio. The alkene synthesis via geminal dihalogenides achieves a much better E:Z ratio (entry 11). If the E:Z ratio has no relevance because one carbon atom of the double bond shows two identical rests, a similar approach using manganese and organic bases represents an alternative (entry 7), however, with a much higher solvent demand. Two identical (aryl) rests at both carbon atoms of the double bond can be achieved by a cis-addition to internal alkynes (entry 8) and thus could be stereoselective while tolerating a variety of functional groups. The other reactions (entries 21, 22, 24, 26, and 27) are stereoselective as well; however, at least one substituent is an aryl rest or contains a carboxylic group, and the solvent demand of the sequence via cyclopropenes (entry 22) is discouraging.

Mass Metrics in General. This examination presents the respective mass performance of different synthetic methods (Figures 1 and 2) for different types of alkenes (Table 3). These various methods we are presenting aim to give an idea of the efficiency that can be expected, however, many other procedures exist in the literature, see relevant reviews regarding Wittig (e.g., refs 103−109), Julia,[110] McMurry,[111−113] other olefination of carbonyl compounds (e.g., refs 114−117), Heck (e.g., ref 118), Negishi (e.g., refs 8, 119, and 120), metathesis (e.g., refs 121 and 122), geminal dihalogenides,[89] and others.[12,123,124]

The results of this examination may support the design of alkene syntheses, for example, in retrosynthetic planning. Of course, if only the receipt of a distinctive alkene in milligram quantities is at the center of interest, our study will not be relevant. However, there is often a desire for efficiency. To the best of our knowledge, there is no other examination that takes a look at such a broad range of syntheses of alkenes with tri- and tetrasubstituted double bonds using green chemistry metrics. The starting materials are qualitatively similar according to the degree of refinement, intending a better comparability of the respective synthesis plan. We demonstrate that, with our software tool,[69] mass metrics can easily be obtained for a single alkene synthesis or synthesis sequences on the basis of a literature protocol or laboratory work.

It has to be clear for all mass efficiency discussions that waste treatment was not considered. Therefore, recycling possibilities might reveal an advantage for a method that was not an obvious choice at first sight according to Figure 1. Additionally, energy aspects could not be considered quantitatively because of missing information. However, the reaction conditions (Table S7) and the actual solvent application (see table in Figure 1 and Table S9 for solvents and their workup) can provide a qualitative clue regarding the potential energy demand. Because of high uncertainties of potential statements, we are not aiming to juxtapose this information but are simply offering it for the reader's interest. In the case of a more in-depth study, it is certainly allowed to appraise "realistic" solvent amounts, and so forth, to determine resource demands and costs. We did this, for example, for a comparison[125] of a biocatalytic versus a chemical synthesis of an enantiomerically pure ß-amino acid. Experiences from the own laboratory can be a point of reference as well as typical literature data, if available. In a fine chemical production, for example, industry reported initial use of 3.3 kg of one solvent and of 4.6 kg of another solvent per kilogram of product, and after recycling, of a final loss of 0.17 kg of the former solvent and 0.6 kg of the other solvent (see Figure 5.13 in ref 68). In the Introduction, we already emphasized the validity of mass metrics compared to life cycle assessment.

Further examples for the utilization of mass metrics (and approaches to consider health, safety, and environment aspects) can be found not only in the professional literature (e.g., bromination reactions,[13,49,126] photochemical transformations,[70,127,128] methylating agents,[129,130] cross-metathesis,[131,132] esterifications,[133,134] substitution reactions,[135,136] reduction reactions,[68,137,138] oxidation reactions,[68,139] asymmetric[68,125,137,140]/biocatalytic[141,142] syntheses, azidation,[143] deprotection,[144] total synthesis,[145] flash chromatography as method[146] and other[68,82,147−167]) but also in chemical didactics.[126,168−174] Further references[175−263] are given in the Supporting Information.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.7b02479.

Data related to the figures, detailed information related to the tables, details of chemical methods, solvent concepts, and assumptions (PDF)

Calculated mass values delivered by the software EATOS, compilation of data, and data from considered literature (XLS)

The EATOS file with all considered syntheses, which is only usable with the EATOS software, is available at http://www.metzger.chemie.uni-oldenburg.de/eatos/ (JAR)

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Notes

The authors declare no competing financial interest.

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