Mass efficiency as metric for the effectiveness of catalysts

Marco Eissen* and Konrad Hungerbühler from the Swiss Federal Institute of Technology in Switzerland,† and Stefan Dirks and Jürgen Metzger from the Universitat Oldenburg in Germany‡ **argue that metrics such as mass intensity, environmental factor and cost index indicate weak points with respect to environmental impact and cost efficiency in synthesis design. These weak points give a precise picture of the progress being made with alternative catalytic systems, and show how, for example, a switching to a heterogeneous system can affect efficiency, both positively and negatively**

Environment- and resource-saving syntheses and processes contribute significantly to sustainable development.[1,2] Catalysis plays an important role and is, therefore, applied frequently in synthesis. Efficient use of resources and lowering costs can be achieved not only by improving the conversion of substrates to a product, but also by recycling the catalyst.[3] Different approaches have been taken to recycling homogeneous catalysts, *e.g.* aqueous systems,[4] fluorous biphase chemistry[5] or multicomponent solvent systems.[6] Another possibility is the immobilization of homogeneous catalysts on a solid support.[7,8] However, maximal recycling of catalyst material should not lose sight of the disadvantages that are potentially connected with it. For example, reverting to environmentally friendly aqueous media always means to include a new compartment in which possibly hazardous substances will be emitted and, thus, a new disposal route to be treated. As well as costs, the intensive production of new alternative (*e.g.* fluoric and ionic[9]) solvents has an impact on the environment, to which even a minimal loss of substances and/or their disposal contribute. Therefore, the fourth of the twelve 'more' green chemistry principles of N. Winterton claims to measure catalyst and solvent losses in air and aqueous effluent.[10] Moreover, a full mass-balance should be established (third principle[10]), which makes use of reagents, auxiliary materials, etc. A holistic view is necessary.[11,12] Mass balances of alternatives can be compared using metrics such as the *E* factor[13] and mass index S^{-1}.[11,14] The *E* factor (ratio of waste [kg] to product unit [kg]) is an output orientated indicator, whereas the mass index S^{-1} (ratio of all raw materials [kg] to the product [kg]) is an input orientated indicator. These metrics and the cost index CI (CURRENCY UNIT per kg product) clarify the benefits and drawbacks of changes in synthesis design, *i.e.* the strong and weak points, which must be addressed.

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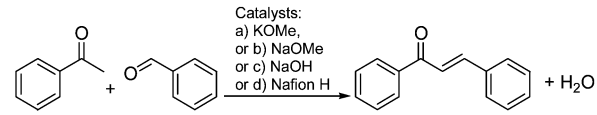
Two examples of important synthesis protocols for carbon-carbon bond formation, aldol condensation and Michael reaction are examined. The aldol reaction of acetophenone and benzaldehyde is usually base-catalyzed, as demonstrated in Scheme 1a) −c).



Scheme 1 Aldol reaction catalyzed by a base (a),[15] (b),[16] (c)[17] or by the recyclable Nafion H (d).

The yields resulting from the use of protocols a) to d) are 75, 71, 85 and 78%, respectively. The base must be neutralized and/or washed out during the work-up procedure. The solid-acid Nafion H,§ on the other hand, can be reused (Scheme 1d).

Fig. 1 shows a quantitative comparison of methods a) to d) (Scheme 1) and, especially, that protocol d) is the most effective procedure with regard to mass efficiency: S^{-1} = 2.7 kg kg^{-1} compared to 5.6 (a), 7.8 (b) and 6.8 (3.0 without water) (c) and E = 1.7 kg kg^{-1} compared to 4.6 (a), 7.0 (b) and 5.8 (2.0 without water) (c). Not only solvents and auxiliary materials can be saved according to protocol d), but the catalyst too, is reusable (at least ten times, therefore, see 'Recycling') without having a negative effect on the yield. This leads to a decrease in

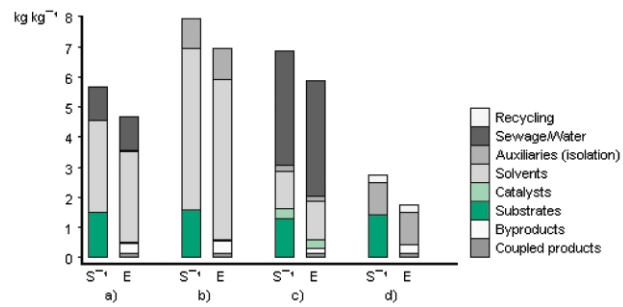


Fig. 1 Mass index S^{-1} and environmental factor E of the a) KOMe, b) NaOMe, c) NaOH and d) Nafion H catalyzed synthesis of chalcone according to Scheme 1 using the software EATOS.[11]

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the E factor to 1.5 kg kg^{-1} in synthesis d). Correspondingly, resources are saved as can be seen from the mass index S^{-1}. It is possible to avoid an additional disposal route, the waste water treatment that will be mandatory especial in synthesis c). To obtain an idea of how to estimate the material costs of raw materials in alternative systems, the cost index CI is used to identify the relevant cost drivers (Fig. 2). If the materials are

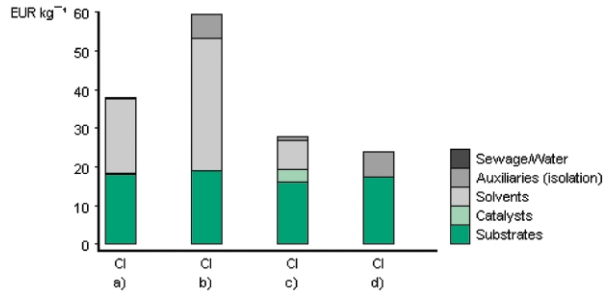
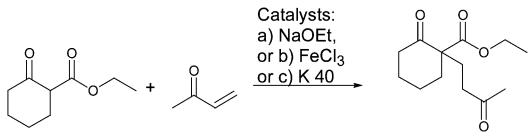


Fig. 2 Cost index CI of the a) KOMe, b) NaOMe, c) NaOH and d) Nafion H catalyzed synthesis of chalcone according to Scheme 1 using the software EATOS.[11]

purchased from Aldrich (see current catalogue) and assuming that Nafion H is recycled, synthesis d) is the most economical (23.7 EUR kg^{-1}). However, because the costs of substrates (d) are slightly higher than in c), measures should be taken to increase yield.

The second example, the Michael-reaction (Scheme 2), can also be base- or Lewis acid- catalyzed. Because procedures a) and b) (Scheme 2) have the disadvantages of catalyst loss in



Scheme 2 Michael reaction catalyzed by a base (a),[15] a Lewis acid (b) or a solid Lewis acid K 40 ($FeCl_3$ supported on montmorillonite) (c).

homogeneous catalysis, the heterogeneous Lewis acid, K 40, a $FeCl_3$-supported montmorillonite, was examined (Scheme 2c). Yields of protocols a) to c) are 70, 85 and 76%, respectively.

According to Fig. 3 protocol a) with S^{-1} = 3.6 kg kg^{-1} requires between twice and three times the amount of raw material as b) and c). Protocol b) avoids a resource intensive

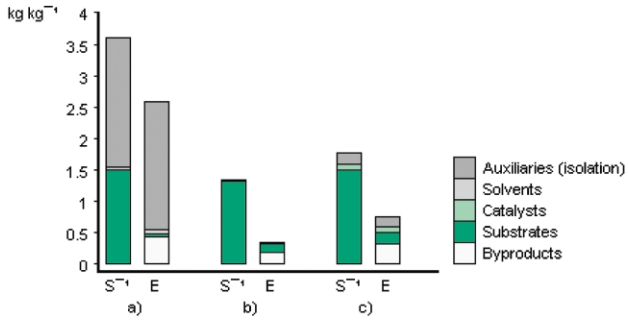


Fig. 3 Mass index S^{-1} and environmental factor E of the a) NaOEt, b) $FeCl_3$ and c) K 40 catalyzed synthesis of ethyl 2-oxo-1-(3-oxo-butyl)-cyclohexanecarboxylate according to Scheme 2 using the software EATOS.[11]

work-up, therefore, the generation of waste (see E factor) is lower by about one order of magnitude compared to a).

The consequence of using protocol c) and implementing a reusable catalyst (K 40) is a decrease in yield as shown in the yellow segment 'Byproducts' in synthesis c). This, of course, has an impact on the amount of substrates necessary to produce one kilogramme of product (compare 'Substrates'). Additional solvents are necessary to extract the product from the catalyst after filtration. Because the activity of the catalyst decreases significantly already in the third run, this catalyst cannot be attributed to the segment 'Recycling' like Nafion H (Fig. 1). Spent K 40 must be disposed of or be treated after a few runs. In contrast, very small amounts of cheap iron(III) chloride are required in synthesis b). Therefore, compared to chemical problems of other catalytic systems, the effort required to save the catalyst in the Michael reaction (Scheme 2) is unjustified.

In conclusion, Nafion H seems to be an efficient catalyst for performing aldol condensation to yield chalcone in an environmentally friendly manner, i.e. avoiding the use of water and reducing the amount of solvent. In contrast, application of K 40 to the Michael reaction has advantages over traditional base catalysis but does not effectuate an increase in mass efficiency, in contrast to the protocol for homogeneous catalysis using iron(III) chloride. These examples demonstrate that the application of alternative catalytic systems must always be looked at from a holistic point of view that takes the full mass-balance into account. In systems more complicated than those described here for demonstration purposes, the integration of preliminary processes will possibly become necessary. For instance, we examined three four-step routes and one three-step route to ethyl (*R*)-2-hydroxy-4-phenylbutyrate, which is an important intermediate in pharmaceutical industry for Angiotensin Converting Enzyme (ACE) inhibitors; *e.g.* Benazepril (Novartis) and Cilazapril (Roche). Interestingly, based on the data available the route showing an overall yield of 50% and an enantiomeric excess of 76% performs better with regard to mass efficiency than an alternative showing a yield and enantiomeric excess of 99%. Main reasons are solvent demand and other substrates than the key-substrate to which the yield refers.[18]

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Notes and references

§ Nafion H (7–9 mesh) and K 40 were obtained from Aldrich and Süd-Chemie, respectively. In one experiment, catalyst bleeding, 'leaching', of $FeCl_3$ was not observed.[19] Products were characterized by ^{1}H NMR and mass spectrometry as well as by comparing their physical properties with those reported in the literature.

Chalcone by means of Nafion H (Scheme 1d): Acetophenone (3 g, 24.96 mmol) and benzaldehyde (2.65 g, 24.96 mmol), both freshly distilled, were stirred for two days at 97 °C in the presence of Nafion H (1 g). Using a Pasteur pipette, the reaction mixture was separated from the Nafion H pellets. The catalyst was washed twice with 2 ml ethanol that was used to crystallize the product. More product was obtained from the mother liquor via crystallization (1.5 ml ethanol) and Kugelrohr distillation (160-170°C, 10^{-1} mbar) to give a total amount of 4.06 g (78%).

Verification of the recyclability of Nafion H in the chalcone synthesis: In presence of Nafion H (0.25 g), benzaldehyde (0.5 g, 4.71 mmol) and acetophenone (0.25 g, 2.08 mmol) were stirred at 105 °C (oil bath) for 8 h. Using a Pasteur pipette, the mixture was removed from the catalyst, which was washed with few acetone. Another nine cycles were performed with the same catalyst. The yields were

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practically identical (75% and 76%).

Ethyl 2-oxo-1-(3-oxo-butyl)-cyclohexanecarboxylate (Scheme 2c, *i.e*. in presence of K 40): In several portions 2-butenone (5.76 g, 82.2 mmol) was added to ethyl 2-oxocyclohexanecarboxylate (9.8 g, 57.6 mmol) containing K 40 (0.98 g). The mixture was stirred for two days at room temperature. The catalyst was filtered off through a fine filter paper and washed with 2 ml of ethanol. The distillation yielded 10.56 g (76%) of the product. The protocol of Scheme 2b was followed[19] as described in the literature.[20]

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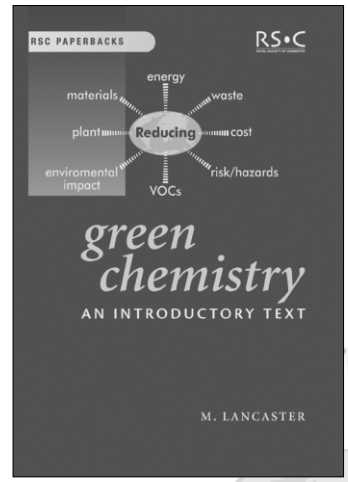

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