

ARCHIVIO ISTITUZIONALE DELLA RICERCA

Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

A translation of the twelve principles of green chemistry to guide the development of cross-coupling reactions

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version: A translation of the twelve principles of green chemistry to guide the development of cross-coupling reactions / T. Fantoni, A. Tolomelli, W. Cabri. - In: CATALYSIS TODAY. - ISSN 0920-5861. - STAMPA. -397:SI(2022), pp. 265-271. [10.1016/j.cattod.2021.09.022]

This version is available at: https://hdl.handle.net/11585/853030 since: 2024-02-12 Published: DOI: http://doi.org/10.1016/j.cattod.2021.09.022

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

(Article begins on next page)

This item was downloaded from IRIS Università di Bologna (https://cris.unibo.it/). When citing, please refer to the published version. This is the final peer-reviewed accepted manuscript of:

A Translation of the Twelve Principles of Green Chemistry to Guide the Development of Cross-Coupling Reactions, Catalysis Today, 2022, 397–399, 265-271

The final published version is available online at: <u>https://doi.org/10.1016/j.cattod.2021.09.022</u>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<u>https://cris.unibo.it/</u>)

When citing, please refer to the published version.

A Translation of the Twelve Principles of Green Chemistry to Guide the Development of Cross-Coupling Reactions

Tommaso Fantoni, Alessandra Tolomelli, Walter Cabri*

Department of Chemistry "Giacomo Ciamician", Alma Mater Studiorum University of Bologna, via Selmi 2 40136-BO Italy

Abstract. In this paper, the applications, impact, and development of green cross-coupling reactions in academia and industry are discussed. Specifically, we discuss the translation of the Twelve Principles of Green Chemistry and their applications in pharmaceutical organometallic chemistry to stimulate the development of cost-effective and sustainable catalytic processes for the synthesis of active pharmaceutical ingredients (API). The evolution of the process for the synthesis of 3-ethylnyl aniline, a key intermediate for the synthesis of the tyrosine kinase inhibitor erlotinib, was described as an example of the application of this translation guide.

Keywords. Heck-Cassar-Sonogashira Reaction · Green chemistry · Sustainability · Process Mass Intensity · Erlotinib

Corresponding author

e-mail address: walter.cabri@unibo.it

1. Introduction

Catalysis, mainly enzymatic and organometallic, is the main alternative to classical stoichiometric chemistry for industrial carbon-carbon bond formation.[1] However, presently, green chemistry approaches must be applied at the beginning of process design. In 1998, Anastas and Wagner [2] translated what could be called "chemical common sense" into The Twelve Principles of Green Chemistry. Their main goal was to inspire the development of industrial chemical synthetic methods. In particular, the 12 principles highlighted the main requirements for the development of safe, cheap, and environmentally friendly methodologies, including the reaction conditions, reagents, and solvents, as well as the use of renewable natural materials and energy, thus defining a "green chemical space." These principles have acted as a development guide/inspiration in the pharmaceutical industry, from drug discovery to industrial production, [3] in which the scientific challenges arising from the increased number of synthetic steps and structural complexity can be tackled using modern techniques. In this context, the ninth principle of green chemistry states as follow: "Catalysis. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents". Many important crosscoupling reactions are utilized in the pharmaceutical sector. Among them, palladium-catalysed reactions, which were first discovered in the 1970s, are currently the most versatile. The main reasons behind the success of these reactions are the very high chemoselectivity and flexibility in terms of substrates, solvents, catalysts, and reaction conditions.[4] However, despite the positive characteristics of organometallic catalysis, a literature review of the main cross-coupling reactions reveals that decades passed before these methodologies became popular in the scientific community (Figure 1).[5] The data in Figure 1, obtained from the SciFinder[©] database, constitutes a comprehensive list of all possible cross-coupling-related studies, including the development of ligands, catalysts, and reaction conditions. This list includes articles, reviews, patents, and synthetic applications. On the other hand, by restricting our search to industrial interest (i.e. limiting the statistics to patents), a similar evolution but on a different scale can be seen (Figure 2). For example, comparison of the two selections shows that patents account for 20% of the approximately 15000 citations concerning the Suzuki cross-coupling reaction received between 2010 and 2020 (see Figures 1 and 2). The different reactions are listed starting from the most popular one: the Suzuki cross coupling. In our opinion, the elegant use of the Suzuki reaction for the industrial synthesis of the first-in-class antihypertensive angiotensin II antagonist losartan [6] by scientists at Merck in the 1990s boosted the development of this reaction methodology, providing new and better catalysts, ligands, and reaction conditions, and ultimately increased efficiency (turnover frequency/turnover number) and reduced environmental impact and costs.



Figure 1. Growth in publications and patents related to cross-coupling reactions.



Figure 2. Growth in patents related to cross-coupling reactions

The reasons for the slow development of these industrially important catalytic reactions are manifold, particularly in the pharmaceutical sector. Clearly, a methodology, once discovered, must reach maturity; however, in the pharmaceutical industry, there are two distinct users with entirely different aims: the medicinal chemist and the process development chemist. The medicinal chemist is focused on identifying the molecular space that must be managed to optimise the interactions with the biological target.[7] Therefore, the synthetic methods should be simple to use, flexible, and potentially applicable to parallel synthesis to enable a rapid increase in molecular diversity. In contrast, in the early stages of clinical development, the process chemist is focused on the chemical space, and the main aim is to deliver a high-quality product at the correct time and lowest possible cost. Only later, for example, when approaching phase III and market approval or during generic competition, aspects related to the environmental impact are fully established. As a result, in 2017, the father of green metrics, Roger Sheldon, complained about the poor attention of the pharmaceutical industry to greening chemical processes,[8] citing several reasons for this apparent antipathy; however, in our opinion, communication gaps and the lack of a common language between different departments inside industrial organizations are the main culprits.

In this article, a translation of the twelve green chemistry principles into practical suggestions for the implementation of catalytic methods is proposed to facilitate the development of pharmaceutical-industry-appropriate synthetic methodologies. The evolution in the synthesis of a key tyrosine kinase inhibitor (erlotinib) intermediate is described as an example of the greening of an industrial synthetic process.

1.1 Catalysis and Green Chemistry

1.1.1 Green Metrics

Since the seminal work on the environmental factor (E-factor) by Sheldon,[9] many green metrics have been introduced. The most useful metric for method optimisation is the process mass intensity (PMI), which is the sum of all the chemicals used to produce 1 kg of final product and includes water and solvents. However, the evaluation of the recovery of all the possible chemicals is critical because it defines the bottom line of raw material cost (RMC) at the industrial level. Therefore, the PMI recalculated after the recovery of all the chemicals (PMIr), which has a direct impact on the production costs, is the best metric for methodology evaluation.

PMI = <u>Σ m (all input materials)</u> m Product PMIr = Σ m (all input materials)- Σ (all recovered chemicals) m Product

Extra synthetic steps such as protection and deprotection have a strong impact on the PMI. Interestingly, palladium-catalysed cross-coupling is highly chemoselective, and a variety of different functional groups are compatible with the reaction conditions. Therefore, a clear factor supporting the choice of organometallic cross coupling reactions when designing a synthetic process is that deviations from the ideality score defined by Baran are not generally determined by the cross-coupling conditions.

%ideality = [(no. of construction rxns)+ (no.of strategic redox rxns) x 100 (Total no of steps)

Another key cost element for process evaluation is plant occupancy, which is directly related to the process time. The full production cost of an active pharmaceutical ingredient (API) is, thus, determined by adding the

costs of plant occupancy (e.g. depreciation, manpower, quality control (QC), and maintenance), energy, and waste management to the RMC. However, the cost of an API is generally not a fundamental element until the new chemical entity (NCE) is under patent, but becomes critical when generic competition starts.

Lipshutz highlighted when using precious-metal-based organometallic catalysts, such as palladium, especially considering their relatively low abundance. [10] Therefore, for the development of new methods based on the twelve principles of green chemistry, the key parameters to be considered are i) PMIr, which accounts for the recovery of chemicals including the metal catalyst; ii) reaction time and temperature; and iii) catalyst performance using the turnover number (TON) and turnover frequency (TOF).

1.1.2 The Twelve green principles: A translation guide for cross-coupling reactions

In pharmaceutical chemistry, the molecular structure of a drug defines the limits of process development because the target structure cannot be changed.

The twelve principles of green chemistry (Figure 3, right and left) were developed to inspire the creation of new processes or methodologies for API synthesis. In fact, all the critical aspects of sustainability were considered by Anastas and Wagner, namely environment (Nos. 1, 2, 3, 5, 7, 8, and 10), health (Nos. 3,4,5), safety (Nos. 5, 11, and 12), and energy optimisation (No. 6). In addition, the overall synthetic strategy (No. 3) and product design (No. 4) were considered, but the only methodology taken into consideration was catalysis (No. 9). Regarding this principle (No. 9, catalysis), in our opinion, the reaction efficiency and recycling potential or catalyst recovery are crucial parameters for greening industrial processes. In this context, TON and TOF are standard parameters that should be enhanced during process development. Therefore, we propose a translation of the twelve principles to inspire the development of efficient and sustainable catalytic protocols at the industrial level. A schematic of the guide is shown in Figure 3, and a full description is given in Table 1.



Figure 3. The Twelve Principles of Green Chemistry. A guide for organometallic chemists.

Table 1. The Twelve Principles of Green Chemistry: a translation guide for catalysis.

THE TWELVE PRINCIPLES OF GREEN CHEMISTRY	TRANSLATION FOR CATALYTIC REACTIONS						
1. Prevention. It is better to prevent waste than to treat	Low PMI and PMIr are preferable. The catalytic reaction						
or clean up waste after it has been created.	should be performed at very high concentrations and the						
	recovery of solvents, chemicals and catalysts should be a						
	target in process design.						
2. Atom Economy. Synthetic methods should be	The catalytic reaction should be optimised by the fine						
designed to maximise incorporation of all materials used	tuning of the reaction conditions to minimise reagent						
in the process into the final product.	excess and achieve high chemo/regio and						
	stereoselectivity.						
3. Less Hazardous Chemical Synthesis. Wherever	Catalytic reactions should be chosen that enable						
practicable, synthetic methods should be designed to use	synthesis based on non-toxic and unreactive substrates.						
and generate substances that possess little or no toxicity	High reactivity is generally associated with high toxicity.						
to human health and to the environment.							
4. Designing Safer Chemicals. Chemical products	Catalysts, solvents, starting materials and auxiliaries						
should be designed to preserve efficacy of function while	should be designed and combined to achieve high						
reducing toxicity.	reaction performances while minimising toxicity.						
5. Safer Solvents & Auxiliary. The use of auxiliary	Catalytic reactions should be performed limiting solvents						
substances (e.g., solvents, separation agents, etc.) should	and auxiliaries and, whenever possible, biogenic						
be made unnecessary wherever possible and, innocuous	sustainable materials should be used.						
when used.							
6. Design for Energy Efficiency. Energy requirements	The best energy efficiency should be achieved by the use						
should be recognised for their environmental and	of highly reactive catalysts to enable fast reactions under						
economic impacts and should be minimised. Synthetic	mild conditions. The reaction temperature should be						
methods should be conducted at ambient temperature	always < 100 °C, preferably < 60 °C and ideally between						
and pressure.	20-35 °C						
7. Use of Renewable Feedstocks. A raw material or	Use of renewable or biogenic materials should be the						
feedstock should be renewable rather than depleting	preferred choice. Concerning precious metal catalyst,						
whenever technically and economically practicable.	recovery is crucial to guarantee sustainability.						
8. Reduce Derivatives. Unnecessary derivatisation (use	The reaction should be highly chemoselective to avoid						
of blocking groups, protection/deprotection, temporary	the introduction of stable or temporary protective						
modification of physical/chemical processes) should be	groups or functional group manipulation.						
minimised or avoided if possible, because such steps							
require additional reagents and can generate waste.							
9. Catalysis. Catalytic reagents (as selective as possible)	The catalytic reaction must be efficient and have a high						
are superior to stoichiometric reagents.	score high TON and TOF using only a relatively small						
	amount (ppm) of catalyst.						
10. Design for Degradation. Chemical products should be	Chemicals used in the catalytic reaction should not						
designed so that at the end of their function they break	accumulate in the environment and should break down						
down into innocuous degradation products and do not	into nontoxic metabolites.						
persist in the environment.							
11. Real Time Analysis for Pollution Prevention.	Real time monitoring to control the formation of						
Analytical methodologies need to be further developed	nazardous substances is based on the complete						
to allow for real-time, in-process monitoring and control	understanding of the mechanism and side product						
prior to the formation of hazardous substances.	The astalistic reaction should for the set of the						
12.Innerently Safer Chemistry for Accident Prevention.	I ne catalytic reaction should focus on the use of mild						
substances and the form of a substance used in a	conditions, avoiding the use of solvents with high flash						
chemical process should be chosen to minimise the	point and sensitive to oxygen.						
potential for chemical accidents, including releases,							
explosions, and fires.							

Palladium-catalysed cross-coupling reactions can easily satisfy some of these principles: high selectivity and stoichiometry allow control of atom economy (No. 2), catalytic transformations are generally based on the use of less hazardous technologies (No. 3), and high chemoselectivity allows the reduction of functional group

manipulation and protective groups (No. 8). By applying the other principles, further methodology design and development can be achieved. In particular, the selection of solvent and auxiliaries while maintaining the catalyst efficiency is a key target.

2. Experimental

2.1 Materials

Commercial reagents (reagent grade, >99%) were used as received without additional purification. *N*-Hydroxyethylpyrrolidone (HEP) is commercially available and was used after degasification.

High-performance liquid chromatography–ultraviolet (HPLC-UV) analysis was performed using an Agilent 1260 InfinityLab instrument. Column: Zorbax[®] SB-C18; particle size, 5 μ m; pore size, 100 Å; length, 250 mm; internal diameter, 4.6 mm. Mobile phase: H2O/CH3CN, 0.5 mL min–1, gradient from 30 to 80% of CH3CN in 8 min, 80% of CH3CN from 8 to 22 min, from 80 to 10% from 22 to 24 min, and 10% from 24 to 30 min; 30 °C; injection volume: 20 μ L.

2.2 Optimized synthesis of 3-ethynyl-aniline 2

In a 50 mL Schlenk purged with N2, the palladium pre-catalyst Pd(ACN)2Cl2 (13.0 mg, 0.05 mmol, 0.2 mol %) and phosphine ligand SPhos (62.0 mg, 0.15 mmol, 0.6%) were dissolved in 10 mL of HEP and water as a co-solvent. The other reagents were then added in the following order: N,N,N',N'-tetramethyl guanidine (3.2 g, 3.45 mL, 27.5 mmol, 1.1 eq), 3-bromo-aniline 4 (4.3 g, 2.7 mL, 25 mmol, 1 eq), and 2-methyl-3-butyn-1-ol 5 (3.1 g, 3.6 mL, 37.5 mmol, 1.5 eq). The reaction mixture was heated to 80 °C in an oil bath and maintained at this temperature with stirring for 12 h. After complete conversion into intermediate 6 (monitored by HPLC-UV at 210 nm), a further 2 mL of water was added and the mixture was extracted with 25 mL of toluene (three times), transferred into a 100-mL round-bottom flask, and directly treated with (NaOH 1.0 g) for the deprotection of the masked acetylene. The mixture was refluxed for 1 h, and the acetone by-product was removed periodically using a Dean-Stark trap. Upon completion, the reaction was cooled to 25°C and 0.3 g of monmortillonite was added. The reaction mixture was then stirred for 15 min at room temperature and subsequently filtered to remove the particles of NaOH and montmorillonite. HEP (from Scheme 3, step (a)) and toluene (from Scheme 3, step (b)) were recovered in 95% yield after distillation under reduced pressure, and product 2 was obtained in 92% yield without purification.

3. Results and Discussion

3.1. Erlotinib and the Heck-Cassar-Sonogashira cross coupling

Erlotinib (1, Scheme 1), a quinazoline derivative that selectively and reversibly inhibits the tyrosine kinase activity of epidermal growth factor (EGFR), was discovered by Pfizer in 1996.[11] After a few years, in the context of Pfizer's acquisition of Warner–Lambert, the company was forced to divest erlotinib to OSI pharmaceuticals, which completed the development process in partnership with Genentech. In 2004, Tarceva® (erlotinib) was launched in the USA for the treatment of advanced non-small-cell lung cancer. Through retrosynthetic analysis (Scheme 1), 3-ethynyl-aniline 2 was identified as the key intermediate, whose backbone includes a C sp2–C sp connection, which is typically the result of the Heck–Cassar–Sonogashira (HCS) cross-coupling (Scheme 2).

Scheme 1. Erlotinib retrosynthesis.



 $X = I, Br, CI, OTf, N_2^{+}$

The use of a protective group on one of the acetylene terminals is necessary for coupling with commercially available 3-bromo-aniline **4**. The preferred acetylene synthon is 2-methyl-2-butyn-1-ol **5** because it is consistently more stable than the alternative trimethylsilyl acetylene.

An important issue in this reaction is the choice of base, which is necessary in stoichiometric quantities for the HCS cross-coupling reaction (Scheme 2), and is sometimes used as a reaction medium. [12] Unfortunately, many bases are toxic, and their use in stoichiometric amounts in the presence of less problematic solvents is preferred.

Scheme 3. 3-Amino phenyl acetylene 2 synthesis.



a) Palladium-catalysed cross-coupling (see Table 2). b) Deprotection step carried out in toluene (133 g/L, 0.65 M) in the presence of NaOH at reflux for 1 h, quantitative yield.

In 1996, Cabri and Oldani filed a patent for the synthesis of 2 based on the use of the Sonogashira protocol with a Pd(0)/Cu(I) catalyst for HCS coupling (Scheme 3 and Table 3, entry 1). [13] The reaction was performed using 0.6 mol% of palladium catalyst, 2.4 mol% of triphenyl phosphine or 1,1'-bis(diphenylphosphino)

ferrocene (DPPF), 0.17 mol% of copper co-catalyst in N,N-dimethyl formamide (DMF) at 70-75 °C in the presence of tetramethyl guanidine (TMG) as a base. The selected base, TMG, has a very high pKa (15.2 in water and 23.3 in acetonitrile) [14] and a greenness score according to GlaxoSmithKline (GSK) scientists[15] higher than those of several popular bases used in HCS coupling (see Table 2).[12] The PMI of this protocol (Scheme 3, step (a)), including the solvent work-up, is 24, and the reaction has some positive aspects, such as stoichiometry, limited excess of base and alkyne, and low amount of palladium catalyst. In addition, TMG is a very efficient base and was chosen at that time (the Sneddon greenness score was published almost 26 years later) mainly because of the reaction efficiency. In this reaction, the solvents and water account for 87% of the PMI, which is typical of pharmaceutical industrial processes.[16] However, the estimated recovery of dichloromethane (DCM), around 70%, did not have a significant impact because the PMIr was still very high. From the point of view of sustainability and green chemistry, the main issue facing this protocol is the use of DMF and DCM. DMF, which is still one of the solvents of choice for palladium-catalysed cross-coupling reactions, [17] is highly toxic, [18] and, in industry, the search for alternatives is active. [19] DCM, in addition to its health concerns, has a relatively low boiling point, and the recycling process, as well as its manipulation, generally results in losses due to the constant release of the solvent to the atmosphere.[19,20] Moreover, the TON of this reaction was 118, but the TOF cannot be determined because the reaction time was not reported. Furthermore, the step for the deprotection of the masked acetylene for all processes in Table 3 requires the use of NaOH in refluxing toluene for 1 h (PMI = 13; PMIr = 2).[21] Clearly, the choice to separate the two coupling and deprotection steps increased the PMI and decreased the greenness of the two reactions. The overall process had a PMI of 53 and a PMIr of 35.

Base	LD50 mg/kg ^a	GSK's greenness score ^b					
TMG	830	7.5					
TEA	730	6.9					
DABCO	700	6.5					
DBU	120-681	7.3					
Diisopropylamine	420	6.9					
nButylamine	372	6.9					
DIPEA	317	6.3					
K ₃ PO ₄	n.a.	7.3					
Cs ₂ CO ₃	n.a.	7.3					

Table 2. Median Lethal Dose (LD₅₀) in rats and GSK greenness score of the most popular bases in the HCS.

^{a.}Data from the ECHA web site, ^{b.} See reference XIV.

Table 3. Comparison of the syntheses of Erlotinib intermediate 2.

Entry	Pre-catalyst	Ligand	Cul	TMG	5	Solvent	Т	t	Yield	TON	TOF	PMI	PMIr
Entry	(mol%)	(mol%)	mol%	(mol%)	equiv		°C	h	%		h ⁻¹		
1	PdCl ₂ (0.6)	PPh ₃ (2.4)	0.17	TMG (1.15)	1.6	DMF	75		71	118	n.a.	53	35
2	Pd(OAc) ₂ (3)	P(0-tol) ₃ (6)	-	DBU (3)	1.24	THF	80	6	86	28	5	1250	669
3	Pd(DPPF)Cl ₂ (2)	-	-	TMG (1.1)	3	HEP	60	3	85	43	14	122	18
4	$Pd(ACN)_2Cl_2(0.2)$	SPhos	-	TMG (1.1)	1.5	HEP/water 9/1	80	12	92	460	38	17	6

Subsequently, Caporale at al. changed the solvent, base, and ligand and eliminated the co-catalyst, thus improving the reaction protocol (Table 3, entry 2).[22] However, the changes did not substantially increase the greenness of the reaction. In particular, tetrahydrofuran (THF) is a source of concern at the industrial level in relation to the environment, health, and safety (EH&S, see principles 12 and 5).[15] In addition, the workup in step (a) was not designed for industrial production and had a negative impact on the PMI (1250) and PMIr (669).The application of our guide based on the twelve principles should lead to the development of a method with lower PMI and PMIr values and allow for increased TON and TOF while using solvents with a higher greenness scores.

In 2020, HEP (which, at the time, was considered a biogenic intermediate for the synthesis of vinyl pyrrolidone), [23] was selected for the development of HCS coupling reactions in green solvents [24] because of its excellent solubilisation performance, a flash point close to 212 °C, and a low acute oral toxicity in rats (median lethal dose (LD50) > 14400 mg/kg). [25] The use of HEP as a solvent and DPPF as a palladium ligand allowed the co-catalyst to be eliminated and increased the yield to 85% (Table 3, entry 3). Unfortunately, the TON/TOF were poor (43/14, respectively). However, the use of toluene as an extraction solvent allowed the deprotection step to be carried out directly, and the PMI was high (122), although the PMIr was comparable to that of the 1996 protocol (Table 3, entries 1 and 3). The main issue of this process was the high dilution of the cross-coupling reaction and the catalyst performance (TON/TOF = 122/18).

The use of Buchwald's ligand SPhos [26] at a higher concentration (from 0.5 to 2.5 M) allowed a reduction in the amount of excess reagent to control the PMI/PMIr (17/6) and achieve better catalyst performance (TON/TOF = 460/28, entries 1–4). This is the most efficient and green process for the production of erlotinib intermediate 2 and is described in the Experimental section.

4. Conclusions and perspectives

A translation of The Twelve Green Chemistry Principles into practical suggestions for catalysis combined with the PMI as a green metric and the TON/TOF values for catalyst efficiency has been reported. These are powerful tools for the greening and optimisation of cross-coupling reactions. We believe that this guide will accelerate the introduction of green catalytic methodologies in the pharmaceutical sector.

The synthesis of an erlotinib intermediate via HCS cross-coupling and its optimisation to develop an efficient, cost-effective, and greener procedure has been described. The fine tuning of the reagent stoichiometry, palladium ligand reaction conditions, and overall solvent recovery process allowed the process mass intensity after recovery (PMIr) to be optimised to 6, thus increasing catalyst performance and achieving a final TON/TOF of 460/38. This example is similar to those of many other reactions applied in pharmaceutical chemistry. In fact, the positive outcome is a result of the use of alternative sustainable and biogenic solvents [27] and more efficient catalysts.

AUTHOR CONTRIBUTION

Walter Cabri performed writing – original draft and conceptualization. Alessandra Tolomelli & Tommaso Fantoni performed writing – review and editing and conceptualization.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

Acknowledgements

We thank for the support Faggi Enrico S.p.A. for catalysts supply. We kindly acknowledge Alma Mater Studiorum University of Bologna for financial support.

References

[1] T. J. Colacot, C. C. C. Johansson Seechurn in Organometallic in Industry, Wiley-VCH; Weinheim (2020).

- [2] P.T. Anastas, J.C. Warner in Green Chemistry: Theory and Practice Oxford University Press, New York (1998).
- [3] W. Cabri, Catalysis Today 140 (2009) 2-10.

[4] a) C. C. C. J. Seechurn, M. O. Kitching, T. J. Colacot, V. Snieckus, Angew. Chem. Int. Ed. 51 (2012) 5062 – 5085. b) A. Dumrath, C. Lübbe, M. Beller, in Palladium-Catalyzed Coupling Reactions: Practical Aspects and Future Developments (Ed: Á. Molnar,) Wiley-VCH: Weinheim (2013), 445–489. c) A. Biffis, P. Centomo, A. Del Zotto, M. Zecca Chem Rev. 118 (2018) 2249–2295. d) F. M. Perna, P. Vitale, V. Capriati, Curr. Opin. Green Sust. Chem. 30 (2021), 100487.

[5] Suzuki-Myaura: a) N. Miyaura, A. Suzuki, J. Chem. Soc. Chem. Commun. (1979) 866 – 867; Heck-Cassar-Sonogashira: b) H.A. Dieck, F.R. Heck, J. Organomet. Chem. (1975) 93, 259–263. c) L. Cassar, Synthesis of aryl-and vinyl-substituted acetylene derivatives by the use of nickel and palladium complexes, J. Organomet. Chem. 93 (1975) 253–257. d) K. Sonogashira, Y. Tohda, N. Hagihara, Tetrahedron Lett. 16 (1975) 4467–4470; Mizoroki-Heck: e) T. Mizoroki, K. Mori, A. Ozaki, Bull. Chem. Soc. Jpn. 44 (1971) 581 – 581. f) R.F. Heck, J. P. Nolley Jr., J. Org. Chem. 14 (1972) 2320-2322; Stille: f) Milstein, J. K. Stille, J. Am. Chem. Soc. 100 (1978) 3636–3638. Buchwald-Hartwig: g) A. S. Guram, S. L. Buchwald, J. Am. Chem. Soc. 116 (1994) 7901–7902. h) F. Paul, J. Patt, J. F. Hartwig, J. Am. Chem. Soc. 116 (1994) 5969–5970; Negishi: h) E. Negishi, A. O. King, N. Okukado, J. Org. Chem. 42 (1977) 1821–1823; Kumada: i) K. Tamao, K. Sumitani, M. Kumada, J. Am. Chem. Soc. 94 (1972) 4374–4376; Hiyama: I) Y. Hatanaka, T. Hiyama, J. Org. Chem. 53 (1988) 918–920.

[6] R. D. Larsen, A. O. King, C. Y. Chen, E. G. Corley, B. S. Foster, F. E. Roberts, C. Yang, D. R. Lieberman, R. A. Reamer, D. M. Tschaen, T. R. Verhoeven, P. J. Reider, Y. S. Lo, L. T. Rossano, A. S. Brookes, D. Meloni, J. R. Moore, J. F. Arnett, J. Org. Chem. 59 (1994) 6391-6394.

[7] G. Schnorrenberg, New Trends in Drug Discovery, in Successful Drug Discovery (Eds J.Fisher, C. Klein, W. E. Childers), Wiley-VCH; Weinheim (2018), vol 3, part 1.

[8] F. Roschangar, J. Colberg, P. J. Dunn, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, D. K. Leahy, I. Mergelsberg, J. L. Tucker, R. A. Sheldonk, C. H. Senanayakea, Green Chem. 19 (2017) 281–285.

[9] a) F. Roschangar, R. A. Sheldon, C. H. Senanayake, Green Chem. 17 (2015) 752–768. b) Roschangar, Y. Zhou, D. J. C. Constable, J. Colberg, D. P. Dickson, P. J. Dunn, M. D. Eastgate, F. Gallou, J. D. Hayler, S. G. Koenig, M. E. Kopach, D. K. Leahy, I. Mergelsberg, U. Scholz, A. G. Smith, M. Henry, J. Mulder, J. Brandenburg, J. R. Dehli, D. R. Fandrick, K. R. Fandrick, F. Gnad-Badouin, G. Zerban, K. Groll, P. T. Anastas, R. A. Sheldons, C. H. Senanayakea, Green Chem. 20 (2018) 2206–2211.

[10] B.H. Lipshutz, Chem. 4 (2018) 2004–2012.

[11] a) Shur, R.C.; Arnold, R.D., US5747498 (1996). b) P. A Tang, M.-S. Tsao, M. J. Moore, Expert Opin. Pharmacother. 7 (2006) 177-193.

[12] a) M. Schilz, H. Plenio, J. Org. Chem. 77 (2012) 2798–2807. b) R.Chinchilla, C. Nájera, Modern Alkyne Chemistry: Catalytic and Atom-Economic Transformations, (Eds.: B. M. Trost, C.-J. Li), Wiley-VCH Verlag GmbH & Co. KGaA. (2015) 269-297. c) D. A. Alonso, A. Baeza, R. Chichilla, C. Gomez, G. Guillena, I. M. Pastor, D. J. Ramon, Catalysts 8 (2018) 202.

[13] W. Cabri, E. Oldani, US5902902 (1998).

[14] T. Ishikawa in Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes and Related Organocatalysts (Eds: T.Ishikawa), John Wiley & Sons, 2009, 93-143.

[15] R. K. Henderson, A. P. Hill, A. M. Redman, H. F. Sneddon, Green Chem. 17 (2015) 945–949.

[16] a) R. K. Henderson, C. Jimenez-Gonzalez, D. J. C. Constable, S. R. Alston, G. G. A. Inglis, G. Fischer, J. Sherwood, S. P. Binksa, A. D. Curzons, Green Chem. 13 (2011) 854-862. b) C. J. Clarke, W. Tu, O. Levers, A. Bröhl, H. J. P. Hallett, Chem. Rev. 118 (2018) 747–800. c) D. Prat, A. Wells, J. Hayler, H. Sneddon, C. R. McElroy, S. Abou-Shehada, P.J. Dunn, Green Chem. 18 (2016) 288-296.

[17] K. L. Wilson, A. R. Kennedy, J. Murray, B. Greatrex, C. Jamieson, A.J.B. Watson, Beilstein J. Org. Chem. 12 (2016) 2005–2011.

[18] a) ECHA reference for DMF: https://echa.europa.eu/it/registration-dossier/-/registered-dossier/13179. The registration that is only referred to European countries is supporting use, storage and transportation of \geq 10 000 to < 100 000 tonnes per annum.

[19] M. C. Bryan, P. J. Dunn, D. Entwistle, F, Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven, F. J. Weiberth, Green Chem. 20 (2018) 5082–5103.

[20] ECHA reference for DCM: https://echa.europa.eu/it/substance-information/ substanceinfo/ 100.000.763.

[21] A. Onopchenko, E. T. Sabourin, C.M. Selwitz, J. Org. Chem. 44 (1979) 1233–1236.

[22] A. Caporale, S. Tartaggia, A. Castellin, O. De Lucchi, Beilstein J. Org. Chem. 10 (2014), 384–393

[23] M.O. Haus, Y. Louven, R. Palkovits, Green Chem. 2019, 21, 6268-6276.

[24] a) L. Ferrazzano, G. Martelli, T. Fantoni, A. Daka, D. Corbisiero, A. Viola, A. Ricci, W. Cabri, A. Tolomelli, Org.Lett. 22 (2020) 3969-3973. b) T. Fantoni, S. Bernardoni, A. Mattellone, G. Martelli, L. Ferrazzano, P. Cantelmi, D. Corbisiero, A: Tolomelli, W. Cabri, F. Vacondio, F. Ferlenghi, M. Mor, Ricci, A. ChemSusChem 14 (2021) 2591–2600.

[25] a) ECHA reference for HEP: https://echa.europa.eu/it/registration-dossier/-/registered-dossier/13179. The registration that is only referred to European countries is supporting use, storage and transportation of \geq 1000 to < 10000 tonnes per annum. b) For the most recent data for LD50 >14400 see: J.M. Ansell, J. A. Fowler, Fd. Chem. Toxic 26 (1988) 475-479.

[26] D. Gelman, S. L. Buchwald, Angew. Chem., Int. Ed. 42 (2003) 5993–5996.

[27] Alternative solvents for HCS coupling. Water: a) G. Herve, C. Len, Sustainable Chem. Processes 3 (2015)
3, 3. Dimethylisosorbide: b) K. L. Wilson, J. Murray, H. F. Sneddon, C. Jamieson, Synlett 29 (2018) 2293–2297.
γ-Valerolactone: c) G. Strappaveccia, L. Luciani, E. Bartollini, A. Marrocchi, F. Pizzo, L. Vaccaro, Green Chem.
17 (2015) 1071–1076. d) Deep eutectic solvents: F. Messa, G. Dilauro, F. M. Perna, P. Vitale, V.Capriati, A.
Salomone, ChemCatChem 12 (2020) 1979–1984.