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Integrated Solutions to Environmental Protection in Process R&D

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Abstract. For the development of eco-efficient processes needed for the manufacturing of pharmaceutical drug substances, Chemical Development in former *Sandoz Pharma* (the described procedures were developed and established in *Sandoz Pharma*, and they will have to be harmonized with the procedures of former *Ciba* and will continue as redefined *Novartis Pharma* practice) has chosen a stepwise approach, whereby the solving of safety and ecological issues is synchronized with the total development process, which includes clinical, pharmacological, and toxicological studies over many years. At the start, when toxicological studies are the prerequisites for any clinical program, and when only the research synthesis is available for scaleup, the emphasis is on speed to deliver the required amount of drug substance for such time-critical activities. Consequently, only the 'unacceptables' (conditions or reagents which pose threats to the environment (safety, ecology, industrial hygiene)) are to be eliminated at this stage. Further down in development time scale, other improvements of the processes (short cuts, alternative synthesis routes, more cost-effective reaction conditions and reagents), including the elimination of 'criticals' (conditions and reagents which are tolerable in smaller amounts but should be eliminated before the final manufacturing process is to be established), are to be undertaken. Before any process step is carried out in the pilot plant, a tailor-made development risk analysis has to be performed where all aspects of safety and ecological considerations are analyzed and resolved. A *Safety & Ecology Newsletter*, a collection of such 'unacceptables' and 'criticals', as well as proven solutions/alternatives for them is periodically published by the Process R&D Group of Chemical Development and is circulated to all chemists of the *Novartis Group* worldwide. This has helped to raise the awareness of such potential problems and their avoidance already at the research level.

Introduction

It is a great challenge for the chemical and pharmaceutical industry to develop mature manufacturing processes efficiently and to remain competitive economically despite ever increasing constraints in regard to safety and environmental issues. For the pharma industry in particular, in order to introduce any new product into the market, additional hurdles concerning GMP (Good Manufacturing Practice), patent protection, and other social economical considerations demand not only innovative products with high medical needs to be developed in the shortest possible time, but also equally innovative processes for their production with possibly little or no change after their registration [1][2].

The Chemical Process Development Model [3]

During the last few years, we have adopted a stepwise approach to process research and development. This takes into account not only the clinical and toxicological requirements, but also integrates the concept of safety and environmental protection throughout the whole development. Accordingly, the need to assure an acceptable practice begins already at the very beginning of the chemical development process, whereby it remains always a constant goal throughout the entire life span of the project.

The following are some of the tasks of Chemical Development in *Novartis Pharma*:

- Transformation of a research synthesis into a manufacturing process which is technically sound and environmentally friendly, and fulfilling all safety and GMP regulations, while remaining economically attractive. This includes the search for alternative synthetic approaches which are amenable to further scaleup.
- Manufacturing of pharmaceutical active ingredients and excipients according to predetermined delivery date, amount and quality for toxicological and clinical studies as well as for the development of the final market dosage form.

The approach which we have taken to accomplish these challenging goals are depicted schematically in *Fig. 1*. Besides the need for an elegant and cost-effective process, the main concerns are the elimination of '*unacceptables*' and '*criticals*'.

- *Unacceptables*: Reaction conditions or reagents which, because of safety, ecology, or technical reasons have to be eliminated, before a production process can be scaled up.
- *Criticals*: Reaction conditions or reagents which should be eliminated, otherwise – because of safety, ecology, or technical reasons – special precautions or equipments have to be deployed before a production process can be scaled up.

At the beginning of process development, 'speed' is the main concern. Little or no active ingredient is available for toxicological and galenical formulation studies, both of which are prerequisites for the start of the decisive clinical phase. At this stage, the only available synthesis normally is the one which has been used for the synthesis of milligrams or, at best, tens of grams of material. Nominally, 1–3 kg are required for 'Batch 1', which is needed within 3–6 months after the decision to begin the development process. *This could mean a scaleup factor of 500–1000!* It is therefore imminent that the research and process chemists have to exchange know-how as early as possible.

In those cases which involve the use of 'unacceptables' in research, where environmental and safety concerns are much less an issue, they *have* to be eliminated so as to allow scaleup in the pilot plant, even for the first batch (Batch 1). 'Criticals',

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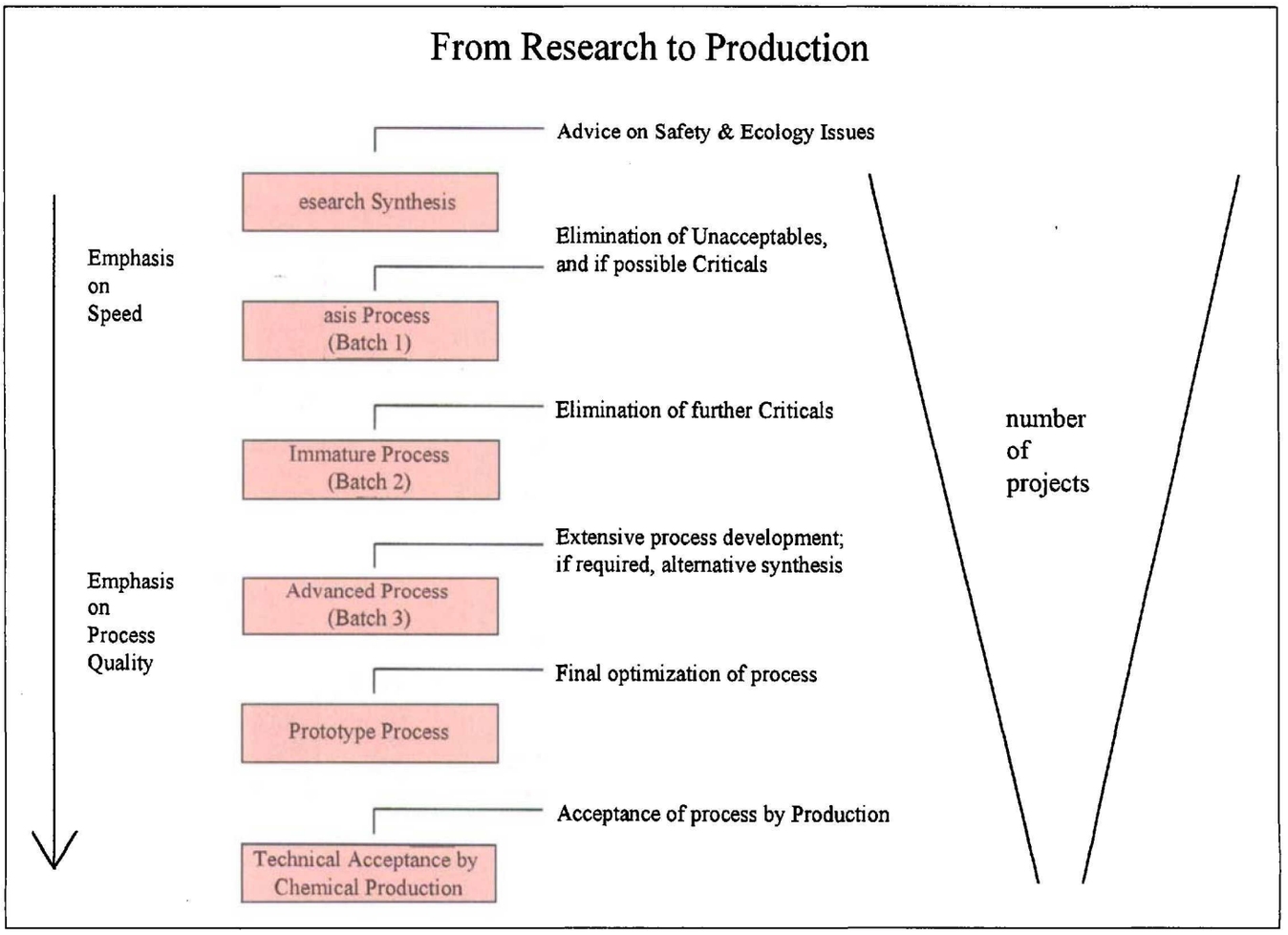

Fig. 1

especially those pertaining to safety issues, require extensive 'safety tests'. In cases where no simple alternatives could be found, new synthetic routes have to be probed in order to circumvent the problems. Alternatively, a toll-manufacturer whose special expertise and equipments allow for an acceptable, noncritical handling of our 'unacceptables' and 'criticals' will have to be contracted. These all take time and will eventually lead to the later start of the clinical phase! In *Tables 1* and *2*, selected 'unacceptables' and 'criticals' are listed.

Therefore, to ensure the timely consideration of safety and environmental issues, the research chemists are encouraged to avoid the use of such 'unacceptables' and 'criticals' when possible even in the small-scale synthesis (a catalogue of such 'unacceptables' and 'criticals' is made available). A number of years ago, the Process R&D group in Chemical Development has initiated the periodical publication of a *Safety & Ecology Newsletter*. This is a collection of such S&E problems which have gone through Chemical Development over the years, and for each of

Table 1

'Unacceptables'	Reasons
Solvents and reagents with flame point < 200° (diethyl ether, acetaldehyde, carbon disulfide)	Dangerous due to inflammable and explosive potential; pilot plants are not allowed to work with such materials
Ethandithiol	Stenching odor; environmental unfriendly and internally forbidden to be used in the *Sandoz* pilot plants
Peracids (*e.g. m*-chloroperbenzoic acid)	Shock-sensitive and highly explosive potential
HN_3	Toxic and explosive; pilot plant does not have the suitable equipment

Table 2

'Criticals'	Reasons
Halogenated solvents	Environmentally unfriendly; special recycling and/or disposal methodologies required
Sodium cyanoborohydride	Acid workup will produce HCN and H_2 and require special handling
Oxidation with chromium(VI) oxide	Disposal problem; heavy-metal contamination likely
Tert. amines (*e.g.* triethylamine)	Non-biodegradable; recovery system required for scaleup

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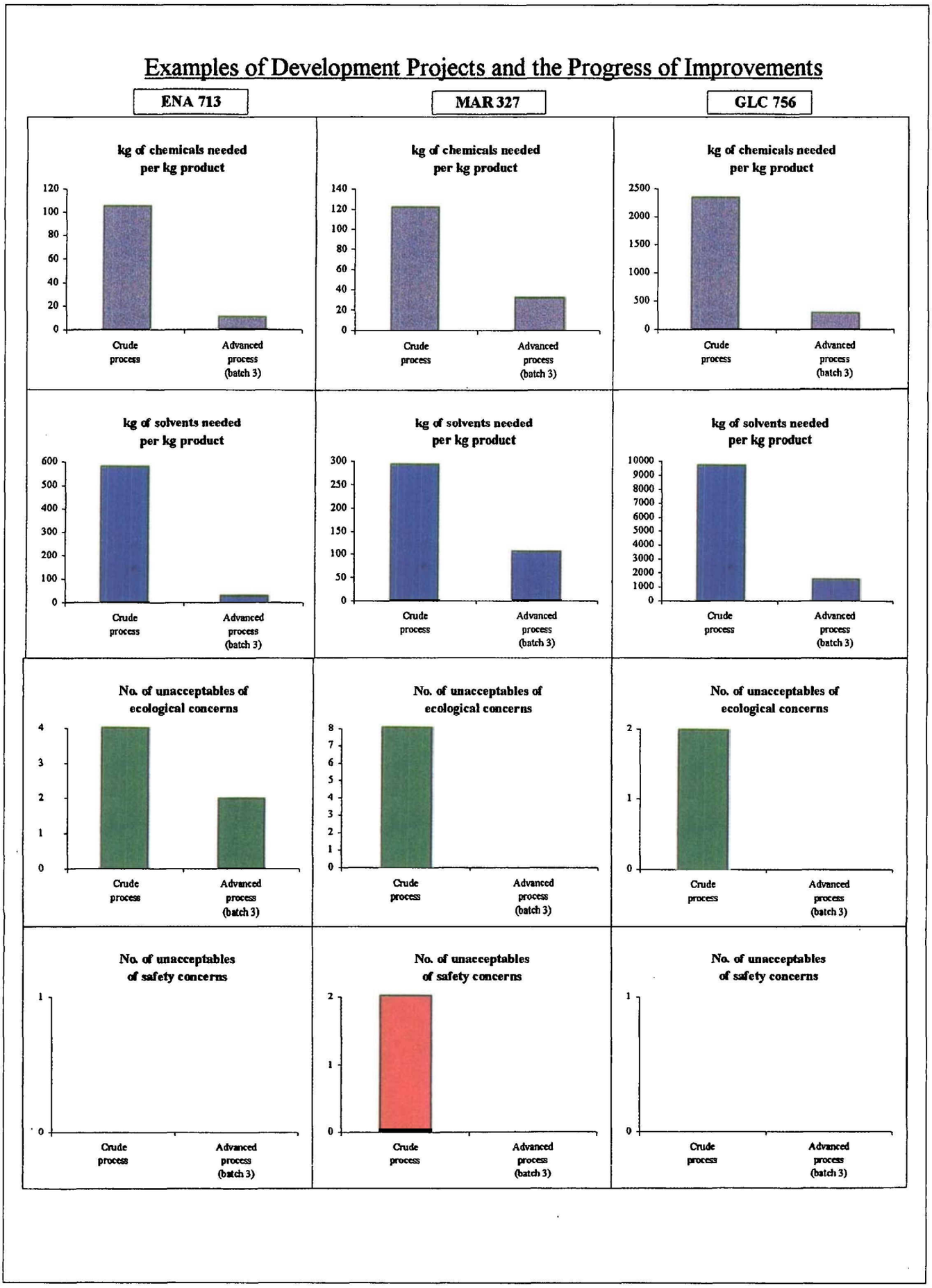


Fig. 2

these, proven alternative(s) are included and discussed.

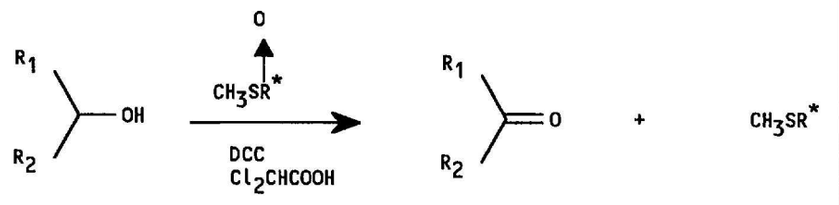
In *Table 3*, a number of examples are shown. These Newsletters were sent to all chemists throughout the *Sandoz Group* (to be continued in *Novartis*). It is not meant to limit the research chemists on their choice of reaction conditions or reagents, but only serves to provide insights into practical solutions which are already available. It is our hope that through wide dissemination of such know-how, the level of safety and ecology awareness could be raised and, in return, less effort would be required to tackle them during the early development phase (as the number of projects at this phase is relatively high, see *Fig. 1*). Consequently, we can produce the Batch 1 much faster and with less resources, which could be made available for other projects, especially those in the later phases, where the chance of introduction into market is higher.

As the general clinical/pharmaceutical development process proceeds further, so is the work in chemical development, where the emphasis changes to 'process quality' (reproducibility, *i.e.* validated process) and process economy. Continuous improvement is being carried out, but also fine process optimization – higher overall yield, less solvent and chemicals needed, and less waste – is the hallmark of these phases and should all contribute to an overall success in eco-efficiency. In *Fig. 2*, three examples of *Sandoz* development compounds are shown to illustrate such process improvements.

Table 3

'Unacceptables'/'Criticals'	Alternatives
$H^+ + Cl^- + CH_2O$ (*e.g. Mannich* reaction) will lead to formation of carcinogenic by-products such as chloromethyl methylether and bis(chloromethyl)ether	Avoid the use of Cl^-, use *e.g.* sulfuric acid as acid source
Sodium cyanoborohydride (reductive amination): highly toxic and forms HCN on acid workup	Sodium borohydride(acetic acid; imine formation/sodium borohydride or H_2/Pd-C
Chromium(VI) oxidation (secondary alcohol → ketone): disposal problems and toxic heavy-metal contamination	$H_2O_2 + Na_2WO_4$ NaOCl/acetic acid
m-chloroperbenzoic acid (epoxidation): shock-sensitive and thermally unstable	1. *N*-bromosuccinimide, 2. NaOH (stereochemistry unimportant)

Scheme 1. *Example of Reagent Design*

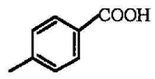


R* = $-CH_3$

Forms the highly volatile, stench odor dimethyl sulfide as by-product in stoichiometric amount

R* = $-(CH_2)_{11}CH_3$

By-product is odorless

R* = 

By-product is crystalline and odorless and easily be recovered and reoxidized to the sulfoxide

Environmental Protecton: Old Chemistry, New Reagents

In some situations, it is easy to avoid the use of certain undesirable solvents (benzene *vs.* toluene), reagents (triethylamine *vs.* tributylamine), or conditions (batch reaction *vs.* addition-controlled semi-batch reaction); in others, where no simple solution could be found, it might require the complete change of synthetic stragegy and thereby creating new intermediates and, unfortunately possibly new profiles in our final product. Therefore, where possible, it might be prudent to retain the original intermediates, even the type of reaction, but modify only the part which contributes to the safety or ecological concerns. In *Scheme 1*, as an example through 'reagent design', we illustrate how the standard *Moffat-Pfitzner* oxidation conditions, which otherwise produce dimethyl sulfide (stench, highly volatile, difficult to be contained), can be carried out without problem on an industrial scale [4].

Environmental Protection: Atom Economy and Catalytic Process

The use of transition-metal catalysts in organic synthesis has shown wide acceptance and has promised to revolutionize the chemical industry, both in terms of high yield (chemical selectivity and specificity) and atom economy [5] (maximum number of atoms of reactants appearing in the products), thereby resulting in little or no waste. We have also been active in this pursuit, and in early screening for alternative methodologies, the possibility to use metal-catalyzed processes is always being sought after. In *Scheme 2*, two successful examples are depicted schematically [8].

Environmental Protection: The Team Approach

Within Chemical Development in *Sandoz* [3], the complex resolution of safety and environmental protection issues in each project has been handled by a team of experts; they included representatives from

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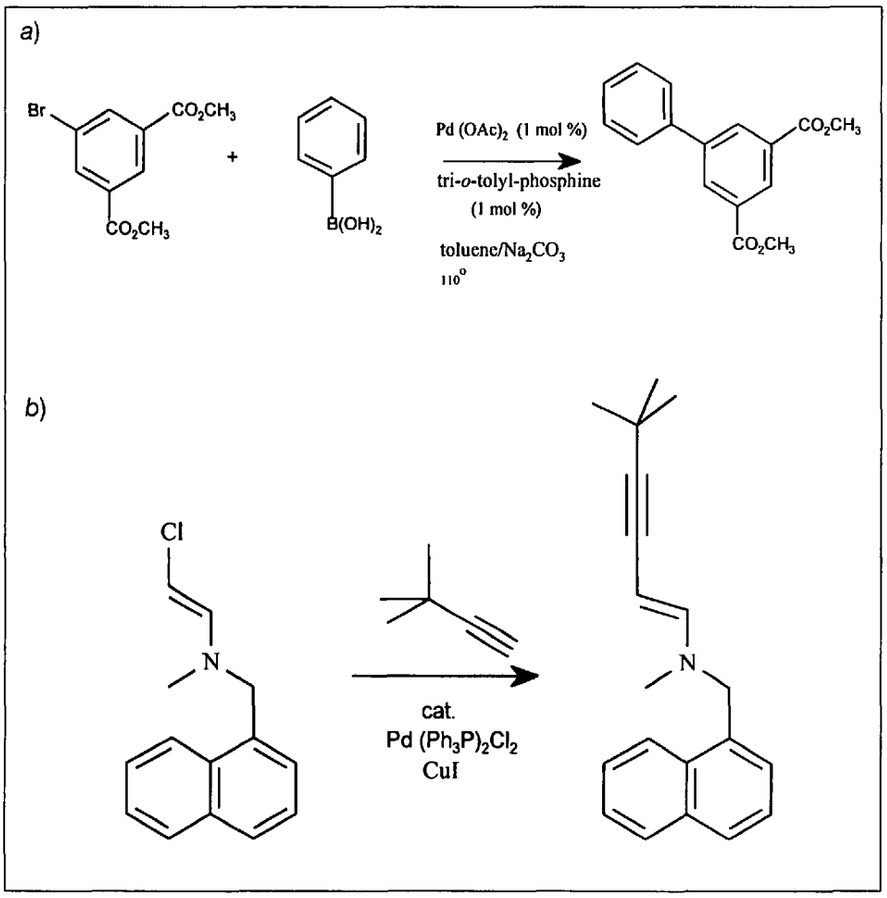
Scheme 2. a) *Palladium*(0)*-catalyzed cross-coupling reaction* (*Suzuki* reaction) *for the preparation of biphenyl derivative is highly regioselective and produces excellent yield (96%) of the decided product with practically no waste.* Solvent and catalyst can easily be recovered [6]. b) *Palladium*(0)*-catalyzed cross-coupling of the alkyne and the vinyl chloride affords the decided product in a stereospecific manner in extremely high efficiency* (96%) [7].



the process labs, pilot plant, safety lab, and a corporate specialist for environmental protection. Before each step would be scaled up in the plant, the detailed process has to be systematically challenged in a risk analysis session, specifically designed for chemical development [9]. All aspects have to be analyzed with respect to safety and ecology compliance to internal and local governmental regulations, and opportunities to improve the eco-efficiency are searched for.

In addition, the involvement of chemical production experts on process-related issues, in particular those pertaining to safety and ecology matters on further upscaling, is institutionalized, and formal discussion takes place after the completion of each pilot-plant batch, starting from the second campaign. In this way, continuous feedback on potential concerns as well as timely improvement is guaranteed.

Conclusion

Despite the ever-increasing constraints that are being imposed upon us, it is our conviction that through full commitment to the pragmatic and integrated approach that we have chosen, the interests of the public and our own can be fulfilled without any compromise.

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[1] G.P. Pisano, S.C. Wheelwright, *Harvard Business Review* **1995**, *September-October*, 93.
[2] G.P. Pisano, S.C. Wheelwright, *Genetic Engineering News* **1996**, 31.
[3] The described procedures were developed and established in *Sandoz Pharma*. They will have to be harmonized with the procedures of former *Ciba* and will continue as redefined *Novartis Pharma* practice.
[4] D. Wasmuth, 'Umweltfreundliche Alkohol-Oxidationen mit aktivierten Sulfiden/Sulfoxiden', Poster presented at the New Swiss Chemical Society Meeting, October 16, 1992.
[5] B.M. Trost, *Angew. Chemie* **1995**, *107*, 285.
[6] W. Mueller, D.A. Lowe, H. Neijd, S. Urwyler, P.L. Herrling, D. Blaser, D. Seebach, *Helv. Chim. Acta* **1992**, *75*, 855; the yield cited therein has since been improved dramatically by Chemical Development.
[7] G. Penn, U. Beutler, D. Wasmuth, B. Schenkel, J. Mazacek, *Chimia* **1996**, *50*, 154.
[8] As can be seen from the example in *Scheme 1*, atom economy is not always possible, but a delicate balance between chemistry, process, and environmental protection is required.
[9] R. Spaar, G. Suter, 'A Simplified Hazard Analysis Scheme for Use in Process Development', Lecture presented at the 7th International Symposium on Loss Prevention and Safety Promotion in the Process Industries, Taormina, Italy, May 4–8, 1992.