



Adriano F. Indolese

Cryogenic lithiation reactions and transition metal catalysis

A synergistic pairing

ADRIANO F. INDOLESE*, KATHRINE GIRLING, MARTIN HAGEN

*Corresponding author

RohnerChem, Gempenstrasse 6, Pratteln, CH-4133, Switzerland

KEYWORDS: Cryogenic lithiation, transition metal catalysis, carbonylation, Suzuki coupling, aryl boronic acid, palladium.

ABSTRACT: Low temperature reactions and transition metal catalysis (TMC) have emerged as powerful tools in organic synthesis in the past few years. Complex aromatic molecules can be easily synthesized by combining the cryogenic lithiation and TMC technologies. The differences and the synergies of these reaction types are discussed in the context of industrial relevant molecules. The specific advantages of the two technologies are demonstrated on examples of the synthesis of benzoic acid and biphenyl derivatives.

INTRODUCTION

The quest for selectivity has always been the major driving force for the advancement throughout the history of chemistry. Selective methods are becoming ever more important with increasing complexity of molecules to synthesise. There are several benefits of highly selective transformations. First of all, fewer side products are formed and therefore higher yields can be achieved. The work-up is simplified. Generally, the isolation and purification of a chemical product is often a more difficult task than performing the chemical transformation. The second benefit of selective reactions is the specific transformation of only one of several functional groups present in the molecule. This allows the synthesis of very complex molecules without protecting group chemistry, resulting in shorter synthesis sequences, higher overall yields, and drastically reduced production costs.

Most chemical companies in business for more than hundred years, RohnerChem included, started with effective but harsh traditional chemistry like nitration, chlorination, or Friedel-Crafts reactions. These methods are still very valuable for the synthesis of simple building blocks which are the starting materials for more complex molecules. With increasing complexity of the target molecules, the chemical industry acquired more advanced and selective methods, e.g. low temperature reactions, catalysed reactions, or hazardous chemistry. RohnerChem, for instance, focused on transition metal catalysis (TMC), cryogenic reactions, and high pressure hydrogenation (Figure 1).

One key success factor for the performance of these advanced technologies is often the quality of the starting

materials, which is determined by the quality of their production process. Traditional chemical transformations are considered to be simple reactions. However, much experience and know how is required to run these reactions safely and successfully on a large scale. Therefore, RohnerChem cultivates traditional organic chemistry in order to control the quality of the starting materials for the more advanced products.

In this manuscript, we will show the synergies between cryogenic lithiation reactions and transition metal catalysis to transform simple starting materials into more advanced intermediates and final products.

SYNTHESIS OF CARBONYL DERIVATIVES

TMC reactions – metal catalysed carbonylation – as well as lithiation reactions can be used for the synthesis of benzoic acid derivatives (Figure 2).

Palladium catalysed carbonylations (1) are very selective and broadly applicable reactions which lead to a wide variety of products. In the carbonylation reaction, an aryl halide, preferentially a bromide or iodide, is converted with ubiquitous nucleophile and carbonmonoxide in presence of a catalytical amount of a palladium phosphine complex. Besides halides, diazonium groups, sulfonates, and triflates can be used as leaving groups. The method is also very well suited to all kinds of heteroaromatic arenes (2). The choice of the nucleophile determines the reaction products. Water or hydroxide ions give benzoic acids, alcohols result in the corresponding esters, and amines result in benzoic amides.

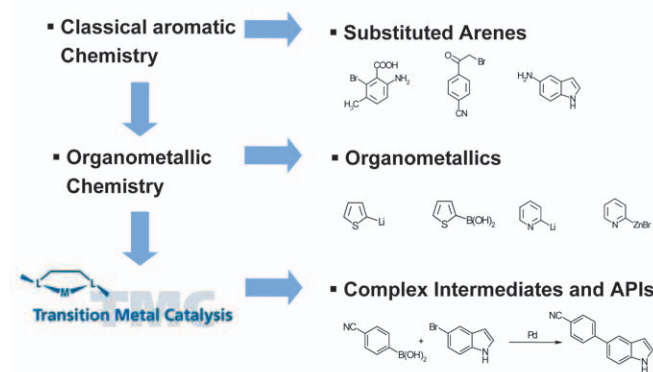


Figure 1. Development of the technology at RohnerChem.

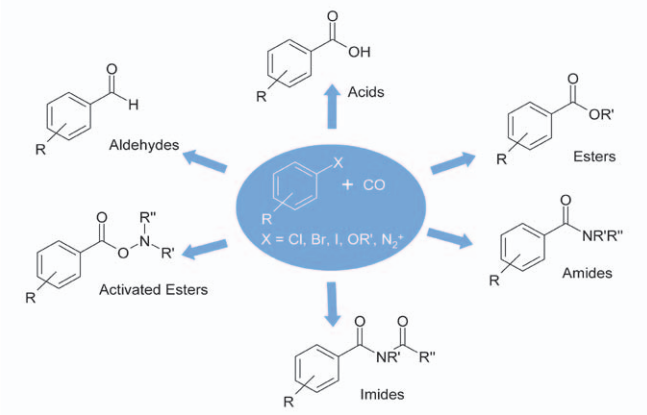


Figure 2. Possible products of the carbonylation reaction.

Under reductive conditions, e.g. in the presence of hydrogen or formate, benzaldehydes are obtained (see ref. (1)). Even very weak nucleophiles such as amides react easily and the corresponding imides are obtained in good yields (3). Due to the mild reaction conditions and the high selectivity, many functional groups are tolerated. Therefore, carbonylation can be applied to highly complex molecules even very late in a synthesis sequence. Carbonylation reactions can be developed quickly and reliably if the required knowledge and experience is available.

Critical issues are, in general, the choice of catalyst and ligand, pressure, solvent, and temperature. As in many catalysed reactions, the quality of the starting material plays an important role in a robust process. Removal of the noble metal from the product is always a challenge. There are many possible approaches, but so far there is no general solution and the issue must be addressed case by case. The handling of carbon monoxide is certainly a challenge on larger scale. It is necessary to have adequate pressure and safety equipment in place. Training and experience of the operators is also a key factor in order to safely handle this highly toxic gas.

When everything is in place, a carbonylation reaction can be developed and scaled up in a very short time, as we demonstrated with the carbonylation to the activated ester using N-hydroxy-succinimide as the nucleophile. (Scheme 1) (4). The reaction was developed and the product was manufactured within four weeks.

The development included catalyst optimization, safety investigations, and investigations to remove palladium below 10 ppm. Lithiation technology can also be used for the synthesis of benzoic acid derivatives.

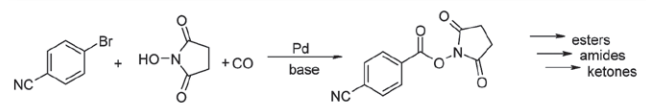
Due to the high reactivity of the lithiated intermediate, the reactions must often be carried out at low temperature and there are some limitations due to the high reactivity of the lithiated species. It can react with the carbonyl group in the product. Most important reactions of lithiated arenes involve carbon dioxide to benzoic esters and amides to aldehydes and ketones. The lithiated intermediate can be

Cryogenic lithiation and transition metal catalysis are a powerful pairing for the synthesis of highly complex molecules. Palladium catalysed carbonylations allow the synthesis of a wide variety of carbonyl compounds in a single step

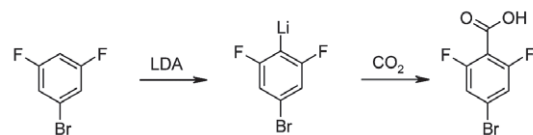
formed either by an halogen / lithium exchange or by abstraction of hydrogen of the aromatic ring (5). The halogen / lithium exchange is carried out with commercially available alkyl lithium reagents. The reaction is clean and fast, even at very low temperatures.

In the case of halogen / lithium exchange, the position of the lithium on the ring is defined. For a selective hydrogen / lithium exchange, a directing group in the aromatic ring is required. The directing group facilitates the abstraction of the hydrogen in the ortho position and stabilizes the lithiated species (6). Alkyl lithium, lithium amides or lithium alkoxides or combination thereof are used for the abstraction of the hydrogen. The choice of the reagents depends on the structure of the substrate and on the other functionalities in the molecule. The reactivity of the reagents is adjusted by the choice of solvent and temperature.

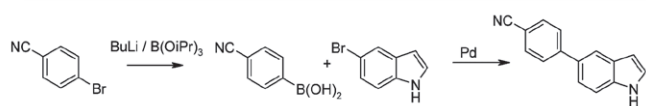
RohnerChem used the cryogenic lithiation reaction for the synthesis of 4-bromo-2,6-difluoro-benzoic acid, which is the starting material for a Suzuki coupling reaction. Due to the bromine in the 4-position, a palladium catalyzed carbonylation could not be applied. The lithiation reaction and the reaction with carbon dioxide worked very well on lab scale and the product was isolated in 73 percent yield with very high purity. For scale up, some challenges had to be overcome. The LDA (lithium diisopropylamide) must be produced freshly from diisopropylamine and butyllithium prior the lithiation reaction. The LDA had to be dosed to the cold solution of 1-bromo-3,5-difluoro-benzene.



Scheme 1. Carbonylation to activated esters.



Scheme 2. Process for the synthesis of 4-bromo-2,6-difluoro-benzoic acid.



Scheme 3. Synthesis of an aryl boronic acid and subsequent Suzuki reaction.

The reaction mixture had to be held below -65°C due to quality and safety reasons. At higher temperatures, a highly exothermic elimination of lithium fluoride occurs leading to the formation of side products and violent decomposition. In order to avoid hot spots during the LDA dosage, the LDA solution must be spread evenly on the surface of the reaction mixture. It was also found on a large scale that the carbon dioxide must be introduced as fast as possible. Otherwise the yields dropped dramatically. With the appropriate measures, the lab results could be reproduced nicely, even on a 2500 L scale.

SYNTHESIS OF BORONIC ACIDS

Palladium and nickel catalysed C-C coupling reactions have become standard reactions in synthetic chemistry. They are widely used in research departments of pharmaceutical and speciality chemical companies. They are the method of choice for the synthesis of many important structural elements which had not been accessible at all by classical organic reactions, or only via cumbersome and tedious routes. An important example is the cross coupling reactions of a metalorganic aryl compound with an aryl halide or pseudo halide for the synthesis of unsymmetrical biaryl compounds. These reactions are catalyzed smoothly and efficiently by palladium and nickel complexes.

Among the different methods, the Suzuki coupling attracted the most attention due to its versatility and ease of application (7). In the Suzuki coupling, aryl boronic acids are employed as the metal organic species. Aryl boronic acids are nicely stable compounds and can be isolated and purified easily. The boronic acids are considered as non-toxic and the boric acid produced in the Suzuki coupling can be disposed off easily.

Some aryl boronic acids are commercially available, but often they must be produced specifically to the needs of the desired compounds. The best and most cost efficient method to produce aryl boronic acids on a large scale is the reaction of the corresponding Grignard or lithium compound with trimethyl or triisopropylborate. After the reaction, the obtained aryl boronic ester is hydrolyzed under basic conditions.

The aryl boronic acid can be isolated, but often the crude solution of the aryl boronic acid can be used directly for the subsequent Suzuki coupling.

RohnerChem used the Suzuki coupling for the synthesis of a complex intermediate (Scheme 3). The 5-brom-indole was produced by Rohner with the traditional chemical know-how. The tricky part was the synthesis of the 4-cyano-benzeneboronic acid. The nitrile group will react with aryl lithium or Grignard compounds.

Therefore, a method similar to Li et al. (8) was developed.

BuLi was added at -65°C to a mixture of the 4-bromobenzonitrile and triisopropylborate. Under these conditions, the bromo / lithium exchange is very fast, forming the aryl lithium species in situ which reacts immediately with the borate ester. Under cryogenic conditions, the desired pathway was much faster than the side reaction of the alkyl or aryl lithium species with the cyano group. The desired aryl boronic acid could be isolated in high yields.

The boronic acid was used successfully in the Suzuki coupling and the aryl indole derivative was isolated in over 70 percent yield. The Suzuki reaction was carried out with only 0.15 percent catalyst which was recovered completely by a charcoal treatment, leaving less than 10 ppm palladium in the product. The process was scaled up to 100 L with no difficulty. Key to the robustness and the reliability of the process was certainly that both starting materials were produced in house and therefore the quality of the materials was under full control.

CONCLUSION

Cryogenic lithiation and transition metal catalysis are powerful tools for the synthesis of highly complex molecules. They are not only very useful on lab scale, but as multiple examples demonstrated, they can be employed on a large scale. The high selectivity of these technologies allows the transformation of highly complex molecules without protection group chemistry. Often shorter and higher yield synthesis sequences can be identified, which allow production with lower costs, less material usage and less waste production. Cryogenic lithiation and TMC are on one hand complementary technologies, but they have also a high synergistic potential.

The application of the technologies clearly requires people with special know-how and experience, and specific apparatus and equipment must be available not only in production but also in the lab. If the prerequisites are met, these reactions can be scaled up and run reliably and safely on a large scale. A key success factor is the quality of the starting materials. In general, it is advantageous to produce the starting materials for the critical step in house. Controlling the whole production chain not only leads to a more robust and reliable processes, but also to rapid advancement of development and scale-up projects.

REFERENCES AND NOTES

1. A. Brennfuehrer, H. Neumann et al., *Angew. Chemie, Int. Ed.*, **48**, pp. 4113-4133 (2009) and references therein.
2. M. Beller, W. Mägerlein et al., *Synthesis*, pp. 1098-1109 (2001).
3. A. Schnyder, A. F. Indolese, *J. Org. Chem.*, **67**, pp. 4311-4315 (2001).
4. A. F. Indolese, D. Wasescha et al., *Chimia*, **59**, pp. 22-24 (2005).
5. M. Schlosser, *Organometallics in Synthesis – a Manual 2nd ed.*, John Wiley & Sons, pp. 1-352 (2002).
6. A.E.H. Wheatley, *Eur. J. Inorg. Chem.*, pp. 3291-3303 (2003) and references therein.
7. a) N. Miyaura, A. Suzuki, *Chem. Rev.*, **95**, pp. 2457-2483 (1995); b) N. Miyaura, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, pp. 41-124 (2004).
8. W. Li, D.P. Nelson et al., *J. Org. Chem.*, **67**, pp. 5394-5397 (2002).