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*Chimia* 51 (1997) 144–146  
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ISSN 0009–4293

# Invention and Development of a Novel Catalytic Process for the Production of a Benzenesulfonic Acid-Building Block

Peter Baumeister<sup>a)</sup>\*, Willy Meyer<sup>b)</sup>, Konrad Oertle<sup>b)</sup>, Gottfried Seifert<sup>b)</sup>, and Heinz Steiner<sup>a)</sup>

(Sandmeyer Prize 1996 of the NSCS)

**Abstract.** Development of a highly 'atom-efficient' production process for 2-alkyl-substituted benzenesulfonic acids by arylation of olefins with 2-diaziobenzene-sulfonate catalyzed by a homogeneous Pd-complex and subsequent hydrogenation of the resulting styrenes with an *in situ* generated heterogeneous Pd-catalyst.

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Konrad Oertle, at that time member of the 'Catalysis Research' group explored the so-called Matsuda [3] reaction (Scheme 1). This reaction type starts from the diazonium salts of aromatic amines as a precursor for the Pd-aryl species. He realized the very broad scope of this reaction and, after optimization of the reaction conditions, synthesized a broad variety of substituted styrenes. This is exemplified by a series of *ortho*-substituted benzenesulfonic acids (Table) obtained from substituted olefins by arylation with 2-diaziobenzene-sulfonate.

## 1. Introduction

Industrial R&D in contrast to research in academia is directed to generate added value for the company and their customers, either by discovery of products with outstanding properties or by finding new and more economic ways to produce these goods. The story to tell is about how catalysis as a *Technology* can facilitate both, the discovery of a new product and the development of a new and economic process.

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Foto: R. Hauck, Basel

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covered by patents from various companies. Long-standing informal contacts between the two chemists facilitated the transfer of know-how and ideas, and since fluorine-containing building blocks seemed to be of particular interest, they agreed to synthesize a series of sulfonylureas. It turned out that several of these sulfonylureas formed a class of potent and highly selective herbicides. The hitherto unknown building blocks available by the newly developed arylation technology made it easy to patent the intermediates and the herbicides found [4]. The sodium 2-(3,3,3-trifluoropropyl)benzenesulfonate was obtained in good yield from the reaction of 2-diazoniobenzenesulfonate with 3,3,3-trifluoroprop-1-ene (Scheme 2). Further lead optimization revealed even better properties for the saturated compound easily obtainable by catalytic hydrogenation of the styrene intermediate.

#### 4. From a Laboratory Procedure to an Economically Feasible Process

The invention of a new and useful product is only the first, albeit a necessary step to innovation. To develop an economically sound process out of a laboratory procedure is in many cases a long way to go. At the beginning of the development work, the willingness to use a hitherto unknown technology in the production was not too widespread in our company and, if a more classical synthesis, e.g. *Friedel-Crafts* alkylation of benzenesulfonic acid, would have proven feasible this route would be chosen. But this way, after considerable work, in accordance to [5], proved to be not effective.

In the agrochemical business manufacturing costs play an important role in the pricing of the product and therefore in the sales volume expected. These manufacturing costs are driven by three factors closely linked to selectivity:

- i) Loss of valuable intermediates in a multistep synthesis due to poor selectivity and the need of supplementary purification steps.
- ii) Necessity to use protecting groups adds as a consequence two supplementary steps to a synthetic route.
- iii) Use of reagents and auxiliary chemicals (solvents, acids, bases) that are not or only partly incorporated in the final molecule are causing waste problems. Unless they are recyclable, they must further be treated to bring them in a disposable form.

A simple way to quantify the efficiency of a synthesis is, according to a recent

Scheme 1. Matsuda Arylation

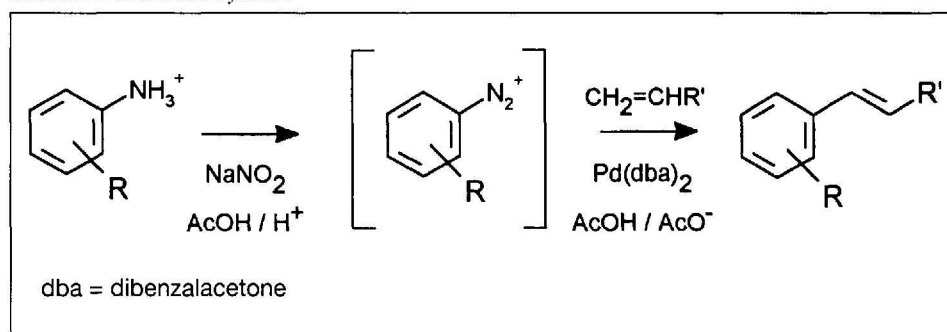


Table. Styrenes by Matsuda Arylation with 2-Diazoniobenzenesulfonate

Olefin	Yield <sup>a)</sup>	Olefin	Yield <sup>a)</sup>
CH <sub>2</sub> =CH <sub>2</sub>	10% <sup>b)</sup>	CH <sub>2</sub> =CHCOOH	87%
CH <sub>2</sub> =CHCH <sub>3</sub>	30% <sup>c)d)</sup>	CH <sub>2</sub> =CHCOCH <sub>3</sub>	85%
CH <sub>2</sub> =C(CH <sub>3</sub> ) <sub>2</sub>	35% <sup>c)</sup>	CH <sub>2</sub> =CHCH <sub>2</sub> OAc	34%
Hex-1-ene	40–45% <sup>c)</sup>	CH <sub>2</sub> =C(CH <sub>3</sub> )COOEt	35% <sup>c)</sup>
C <sub>6</sub> H <sub>5</sub> CH=CH <sub>2</sub>	76%	CH <sub>2</sub> =CHCH <sub>2</sub> CN	20%
<i>o</i> -Br-C <sub>6</sub> H <sub>4</sub> CH=CH <sub>2</sub>	59%	CH <sub>2</sub> =CHCF <sub>3</sub>	85%
<i>p</i> -Br-C <sub>6</sub> H <sub>4</sub> CH=CH <sub>2</sub>	78%	CH <sub>2</sub> =CHCF <sub>2</sub> CF <sub>2</sub> CF <sub>3</sub>	53%
<i>p</i> -F-C <sub>6</sub> H <sub>4</sub> CH=CH <sub>2</sub>	64%	CH <sub>2</sub> =CHSi(CH <sub>3</sub> ) <sub>3</sub>	61%
<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> CH=CH <sub>2</sub>	56%	CH <sub>2</sub> =C(CF <sub>3</sub> )CH <sub>2</sub> CF <sub>3</sub>	44%
<i>p</i> -C <sub>6</sub> F <sub>5</sub> -C <sub>6</sub> H <sub>4</sub> CH=CH <sub>2</sub>	67%	CH <sub>2</sub> =C(CF <sub>3</sub> ) <sub>2</sub>	17%
<i>o</i> -CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> CH=CH <sub>2</sub>	>68%	CH <sub>2</sub> =CHPO(OBu) <sub>2</sub>	61%
<i>m</i> -CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> CH=CH <sub>2</sub>	70%	CH <sub>2</sub> =CHCH <sub>2</sub> PO(OEt) <sub>2</sub>	16%
<i>p</i> -CH <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> CH=CH <sub>2</sub>	82%	CH <sub>2</sub> =CHCH <sub>2</sub> PO(OEt)CH <sub>3</sub>	57%
CH <sub>2</sub> =CHCOOEt	55%	CH <sub>2</sub> =CHSO <sub>3</sub> -C <sub>6</sub> H <sub>5</sub>	41% <sup>c)</sup>

<sup>a)</sup> Yield of isolated sulfonamide after derivatization by known methods.

<sup>b)</sup> 42% bisarylated product.

<sup>c)</sup> Yield after hydrogenation of double-bond isomers.

<sup>d)</sup> Mixture of isomers.

publication of *R.A. Sheldon* [6], the so-called E-Factor (kg by-products or other wastes/kg product).

The task was to develop a highly selective process integrated over as many steps as possible using a minimum of chemicals not directly involved in the stoichiometry of the reaction. This task was mastered by our colleagues working in the 'Chemical Process Development Department Agro'. The process, starting with 2-aminobenzenesulfonic acid and ending with sodium 2-(3,3,3-trifluoropropyl)benzenesulfonate, produces only 2 kg wastes/kg product over the three consecutive synthetic steps equal to an E-Factor of 2. Moreover, the yield over these three steps is 93%, i.e., an average of 98% per step.

One of the important parameters to adjust was it to chose a suitable solvent for the reaction. This solvent was expected to fulfill the following three requirements:

- i) to be compatible with three different chemical reactions;

- ii) to have good solvating properties for the olefin in order to avoid the olefin from being stripped of the reaction medium by the nitrogen formed. Thus avoiding the use of pressure equipment;

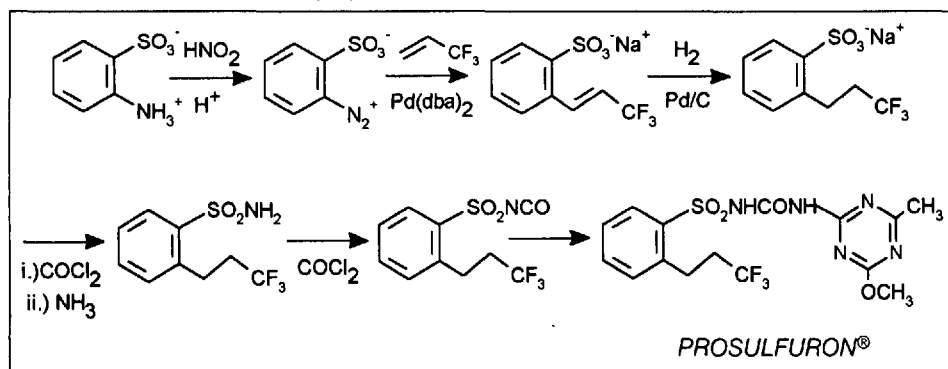
- iii) to be nontoxic and easy to regenerate.

Pentan-1-ol showed the above properties to a high degree. Although the compatibility with the arylation step was not obvious, since *Matsuda* [7] stated alcohols to be unsuitable solvents.

#### 5. Economy of the Palladium-Metal Cycle

Crucial to the overall economy of the process was the economy of the palladium-metal cycle. The productivity, measured in turnovers (TON: number of substrate molecules reacted per atom of Pd), and the activity, measured in turnovers per hour (turnover frequency TOF), of the

Scheme 2. Reaction Scheme Sulfonylurea



catalytic system in the arylation step is rather low (TOF 30–50; TON: 100–200). To attain complete conversion in a reasonable time, the loading of the catalyst precursor is rather high (e.g. 0.5–1.5 mole%). There are in principle two different approaches to optimize the economy of the catalyst usage:

- To make the catalyst more active or more productive, i.e., to either find better precursors forming a catalyst species with higher intrinsic activity, finding ligands providing a better environment for the catalytic entity, or to prevent deactivation of the catalytic species.
- To optimize not only the in-process performance of the catalyst, but to save costs in all the relevant steps from purchasing of the Pd-compound from the Pd-refinery to the recovery of the Pd from the spent catalyst.

The cost-relevant steps for the two catalytic steps in our process are:

**Pd-Salt:** The price of the Pd-compound purchased from the supplier of precious-metal compounds.

**Pd-Precursor:** The costs to manufacture a suitable Pd-precursor from the Pd-compound bought.

**Separation:** The costs for the separation of the homogeneous Pd-complex from the reaction mixture.

**Hydrogenation catalyst:** The price for the hydrogenation catalyst.

**Separation:** The separation costs for the hydrogenation catalyst.

**Pd-Recovery:** The recovery costs for the Pd-metal out of the spent catalyst sent for workup to the refinery.

**Pd-Losses:** The costs to replace the Pd-metal lost in the process and during Pd-recovery.

**Capital costs:** The value of the total Pd-inventory, necessary to aliment the supplying and consumptive cycle, must be treated as an interest-bearing capital investment.

Lacking better alternatives, we did chose the second approach of optimiza-

tion to bring catalyst usage costs to an acceptable level, namely:

**Pd-Salt:** The cheapest form is a solution of  $H_2PdCl_4$  in water, available in various concentrations as a commodity.

**Pd-Precursor:** Pd(dba)<sub>2</sub> proved to be a good precursor for our reaction and could easily be synthesized without any Pd-loss in analogy to the literature [8][9].

The costs for the separation of the homogeneous catalyst and the additional costs for the hydrogenation catalysts could be eliminated by a simple observation. After the completion of the arylation step, the addition of an amount of charcoal to the reaction mixture and stirring under a hydrogen atmosphere generated *in situ* a Pd-on-charcoal catalyst active to bring about the subsequent hydrogenation step. At the end of the hydrogenation, virtually all the Pd was bound to the charcoal and could be filtered off from the reaction mixture. A simple solution for an otherwise quite complex problem.

**Pd-Recovery:** The Pd is recovered by the same operation as usual for a used Pd-on-charcoal catalyst.

**Pd-Losses:** The Pd-metal losses to be replaced are ca. 5% of the amount cycled through the whole process. These losses may be considered reasonable regarding processing in a 'multipurpose plant'.

**Capital costs:** Can be influenced only to the extent that the time lag between the ordering of the Pd-salt and the termination of the workup of the spent catalyst is minimized.

The result of this integrated cost-saving approach are catalyst costs that are by no means low, but in an acceptable range regarding the value of the product. The whole production process was finally patented [10].

## 6. Production and Commercialization

It is absolutely clear, that after a successful development of a process in the laboratory the story of innovation is not at

an end. A lot of work by competent people in production, logistics, and marketing is still needed to complete the success story of a product and at the end, the product must still be accepted by the customer.

## 7. Conclusions

This case study tells the story of both, product and process innovation brought about by the application of catalytic technology.

- The accessibility of an intermediate, not available economically by more conventional synthetic methods, has been changed by the application of a novel catalytic method. This cleared the way for a rare example of technology-driven product discovery.
- The skillful combination of different catalytic and noncatalytic steps to a high-performing process is exemplified in the present work.

The authors are well aware that the success of the project depended to a high degree on valuable contributions made by colleagues not explicitly named in this article and on the continuous encouragement by peers. In particular we would like to thank *H. Landert* and *B. Jau* for their skillful experimental work done on the *Matsuda* arylation and the synthesis of the sulfonylurea, *U. Siegrist* for contributing in the initial development of the arylation step, *R. Lang* for coaching the team in the early development stage, *K. Coers*, *H.-D. Schneider*, *J. Kulka*, *D. Borer*, *A. Semadeni* for their outstanding contributions to develop the process to the plant scale.

Received: February 21, 1997

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