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Journal of Organometallic Chemistry 653 (2002) 288–291
Journal of Organometallic Chemistry
www.elsevier.com/locate/jorganchem

Mini Review

Some applications of the Grignard cross-coupling reaction in the industrial field

Tadashi Banno *, Yoshiki Hayakawa, Masayuki Umeno

Fine Chemicals Research Laboratories, Hokko Chemical Industry Co., Ltd, Toda 2165, Atsugi 243-0023, Japan

Received 28 July 2001; received in revised form 10 January 2002; accepted 16 January 2002

Abstract

We have been offering various fine chemical products used in a wide range of industrial fields by accumulated Grignard reaction technology. The prodcut, which we manufactured first in 1984 by the Grignard cross-coupling reaction, was *p*-chlorostyrene (PCST). PCST is useful as a raw material for functional polymers and synthetic reagents. For the industrialization of PCST, we used the nickel-phophine catalyzed cross-coupling reaction reported by Kumada and Tamao in 1972. We have been manufacturing various kinds of compounds using cross-coupling reaction after development of PCST. In this paper, we describe four types of the Grignard cross-coupling reactions currently carried out in our company. In addition, we show the plant performing the Grignard cross-coupling reaction, and describe the manufacturing process. © 2002 Published by Elsevier Science B.V.

Keywords: Grignard; Cross-coupling reaction; Chemical products

1. Introduction

Since the Grignard cross-coupling reaction was reported by Kumada and Tamao [1] as well as Corriu and Masse [2] in 1972, it has been used in wide range of industrial fields. It has proved extremely efficient for the application to manufacture a variety of fine chemical products, such as pharmaceuticals, agrochemicals, electronics, resins and so on. We have a history of performing the Grignard reaction industrially for about 50 years. In recent years, the importance of the Grignard cross-coupling reaction has been greatly increasing as the industrial process in our company. In this paper, we describe current applications of this reaction in the industrial field.

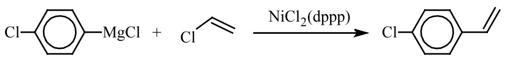
2. Industrialized cross-coupling reactions

There are four types of the Grignard cross-coupling reaction currently carried out in our company as listed below.

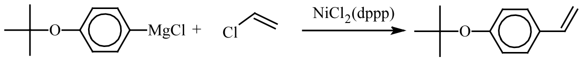
1. The reaction between an aromatic Grignard reagent and an alkenyl halide.
2. The reaction between an aromatic Grignard reagent and an alkyl halide.
3. The reaction between an alkyl Grignard reagent and an aromatic halide.
4. The reactions between an aromatic Grignard reagent and an aromatic halide.

2.1. The reaction between an aromatic Grignard reagent and an alkenyl halide

We industrialized the reaction reported by Kumada and Tamao in 1972. It is the reaction using a nickel–phosphine complex as a catalyst. Specifically, we industrialized the styrene compounds as illustrated in Eqs. (1) and (2):



(1)



(2)

In industrialization of *p*-chlorostyrene (PCST), we found a specific solvent effect. In the original paper [1],

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* Corresponding author. Fax: +81-46-2297058.
E-mail addresses: banno-t@hokkochem.co.jp (T. Banno), hayakawa-y@hokkochem.co.jp (Y. Hayakawa), umeno-m@hokkochem.co.jp (M. Umeno).

0022-328X/02/$ - see front matter © 2002 Published by Elsevier Science B.V.
PII: S0022-328X(02)01165-8

vinyl chloride was reacted with the Grignard reagent of *p*-bromochlorobenzene in ethyl ether. However, in order to establish a high yield and safe industrial process for PCST using low-cost materials, we tried to use THF as a solvent instead of ethyl ether, and *p*-dichlorobenzene instead of *p*-bromochlorobenzene. When this cross-coupling reaction was carried out in THF only, the reaction proceeded slowly, and only low yield was attained. When vinyl bromide was used instead of vinyl chloride, better yield was obtained. However, when an aromatic solvent such as toluene and benzene was added, the yield was increased dramatically. The best result was obtained when THF was used as a co-solvent in benzene or toluene in 2.2–2.4 mol-equivalents to the quantity of *p*-dichlorobenzene [3]. Representative results are summarized in Table 1.

A similar negative effect of THF was also reported by Tamao and Kumada [1]. From those results, it is supposed that THF tends to coordinate to the nickel catalyst stronger than the substrate vinyl chloride. The PCST is useful as a raw material for functional polymers and synthetic reagent. We are producing it about 5000 kg per year.

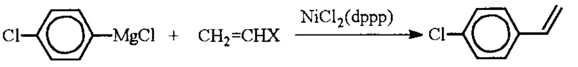
p-*tert*-Butoxystyrene (PTBST) as illustrated in Eq. (2) is also manufactured by a similar cross-coupling reaction to PCST. We started to manufacture PTBST on a commercial basis in 1988. Recently, the production volume is increasing, because it has been attracting much attention as a raw material of photoresist. We are manufacturing it about 200 000 kg in a year.

As described above, the cross-coupling reaction using a nickel–phosphine catalyst is very suitable for manufacturing of styrene compounds. DPPP (1,3-bis-(diphenylphosphino)propane) or DPPB (1,4-bis-(diphenylphosphino)butane) is often used as the best ligand.

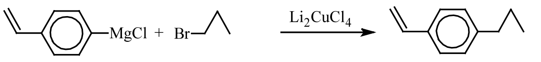
2.2. The reaction between an aromatic Grignard reagent and an alkyl halide

We often use CuCl or Li_2CuCl_4 [4] as a cross-coupling catalyst industrially. The example of the reaction is shown in Eqs. (3) and (4).

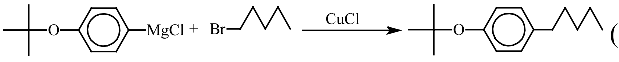
Table 1
Solvent effect in the formation of PCST



Run	Solvent	Molar ratio THF/ArMgCl	X	Yield (%)
1	Et_2O	6	Br	56
2	THF	6	Cl	5
3	THF/toluene	2.2	Cl	63
4	THF/benzene	2.2	Cl	68



(3)



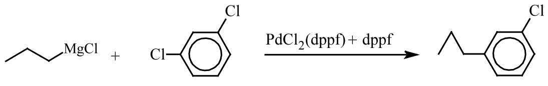
(4)

A variety of functional monomers are manufactured by carrying out the cross-coupling reaction further with Grignard reagent of PCST prepared above. Moreover, the precursors of various phenol compounds are manufactured by the copper-catalyzed cross-coupling reaction of *p*-*tert*-butoxyphenylmagnesium chloride with alkyl bromides. They are useful as intermediates for pharmaceuticals and liquid crystals. The subject in the case of using copper catalysts is that much quantity is required compared with nickel catalysts or palladium catalysts.

2.3. The reaction between an alkyl Grignard reagent and an aromatic halide

Usually, when a nickel–phosphine catalyst is used, the title reaction proceeds successfully. However, we observed that the reaction using an aromatic halide substituted an alkoxy group did not proceed sufficiently. In such a case, we choose the reaction between an aromatic Grignard reagent and alkyl halide as already described.

In this type of the reaction, we developed the Grignard cross-coupling reaction with dichlorobenzenes to produce mono-alkylated benzenes selectively [5] as illustrated in Eq. (5).



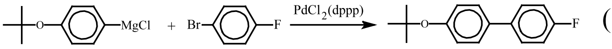
(5)

Usually, the cross-coupling reaction between a dichlorobenzene and an alkyl Grignard reagent using a conventional nickel catalyst provides a di-alkylated benzene predominantly [6]. $[NiCl(triphos)]PF_6$ [7] and $Ni(acac)_2$ [8] has been known as the catalyst of mono-alkylation. However, they did not always give satisfactory selectivity. It was also reported that di-halobenzenes such as fluorochlorobenzene, bromochlorobenzene, and dibromobenzene lead to mono-alkylbenzenes by using a palladium catalyst [9], but the reaction with a dichlorobenzene does not work well under a similar condition.

We found that the Grignard cross-coupling reaction catalyzed by certain palladium–phosphine complexes gave rise to the selective formation of mono-alkylated benzenes from dichlorobenzenes. Among various ligands examined, 1,1′-bis(diphenylphosphino)ferrocene (DPPF) was formed to be the most effective ligand. The highest yield was attained by adding excess DPPF to palladium in the range of DPPF: Pd = 2:1–3:1. A variety of *p*- or *m*- substituted chlorobenzenes are produced by this method.

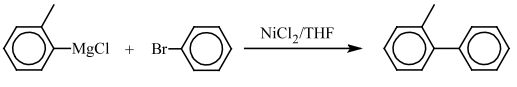
2.4. The reaction between an aromatic Grignard reagent and an aromatic halide

We are manufacturing some biphenyl compounds as illustrated in Eq. (6). The biphenyl derivative shown here is a precursor for liquid crystals and pharmaceuticals.



(6)

In many cases, it is necessary to use aryl bromides as halide and palladium complexes as catalyst for obtaining good yields in this Grignard cross-coupling reaction. In order to avoid such a high cost condition, we are still trying to develop a low-cost process, which uses a chloride as substrate and a low-cost catalyst other than palladium. The non-ligated nickel dichloride catalyzed cross-coupling reaction as illustrated in Eq. (7) [10] would be a good candidate for a practically useful low-cost procedure.



(7)

The formation of homo-coupled biphenyl derivatives as by-products often becomes an obstacle in the purification process of the cross-coupled main product. The combination of the aryl Grignard reagent and aryl bromide is related to this problem. Thus, it is important for an industrial process to find a best combination by careful checking which one of two aryl halides should be use as a Grignard reagent.

We also use the Suzuki–Miyaura reaction industrially [11]. This reaction is useful to produce biphenyl compounds, which have substituents incompatible with Grignard reagents.

3. Production facility of the Grignard reaction

The Grignard cross-coupling reaction is performed industrially at the plant as shown in Fig. 1.

We have glass-lined and stainless steel reactors with the capacity of 1000 to 15 000 l. Each product is manufactured efficiently in one of eight plants that are well suited to its manufacturing process and quantity. Many of our products are manufactured using the Grignard reaction. The Grignard reaction can be performed in all of our plants.

Basically, the producing process consists of four unit processes which include the formation process of the Grignard reagent, the Grignard reaction process, hydrolysis and aftertreatment process, and concentration process. Each process uses an individual reactor vessel. In addition, the solvent recovery process and other concomitant processes are performed to complete the whole manufacturing process.

Fig. 1. Glass-lined reactors.

3.1. Process 1: formation of Grignard reagent

We use a stainless steel reactor in the formation of the Grignard reagent as shown in Fig. 2.

Magnesium is employed in the form of thin turnings; 200–300 kg of magnesium is used for a lot in the scale of 6000 l vessel. We have our own know-how of activating method of magnesium. The concentration of the Grignard reagent is determined by consideration of the workability.

3.2. Process 2: Grignard cross-coupling reaction process

The cross-coupling reaction is performed by successive addition of a catalyst and a halide to the Grignard reagent transferred from the previous reactor. In the case of the reaction with vinyl chloride for the production of PTBST, the gaseous vinyl chloride is blown through the reaction mass. The reactor adjusts the appropriate temperature. Our reactors can be heated to 150 °C with steam, and can also be cooled to − 10 °C using brine.

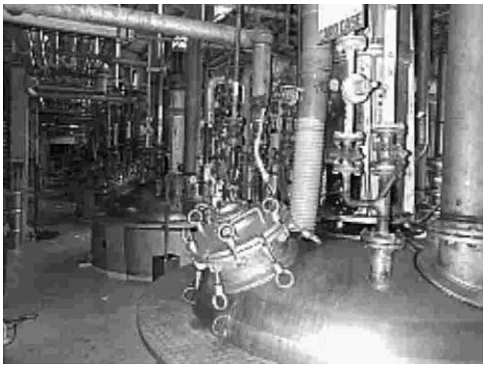


Fig. 2. Stainless steel reactors.

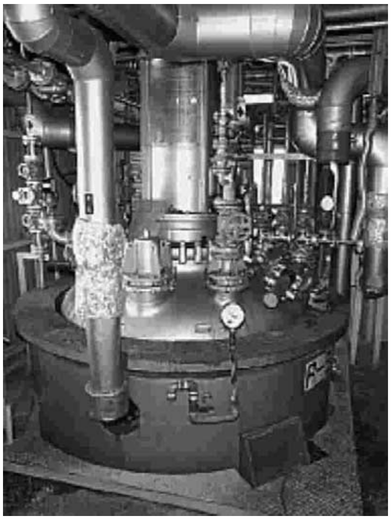


Fig. 3. A vessel for concentration.

3.3. Process 3: hydrolysis and aftertreatment process

Hydrolysis process is highly exothermic and must be performed carefully in order to avoid a rapid rise of temperature. The catalyst is removed as an aqueous layer. Solvent is recovered also from the aqueous layer, and finally the aqueous layer is sent to the wastewater treatment facility.

3.4. Process 4: concentration process

Concentration of the organic layer is carried out at atmospheric pressure or under reduced pressure using another vessel as shown in Fig. 3.

Recovered solvent was reused after purification and drying. Management of the solvent is one of the most important works in industrialization of the Grignard reaction. We have also made it possible to recycle the solvent, especially THF, efficiently by our long term experiences and original know-hows.

4. Progress towards the future

The Grignard reaction is steadily increasing its industrial importance as the modern technology for production of a variety of compounds. Many companies have recently been trying to use this technology and to increase their share in this field. Under such circumstances, we also have to improve our technology without delay. Among many issues to be improved, all kinds of environmental concerns are of the first priority. For this purpose, we are going to strive for developing the catalyst-recovery or recycling and the perfect reaction conditions with no organic by-product in our Grignard cross-coupling manufacture.

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