EXAMINATION OF REACTIONS CATALYZED BY SOLID BASES

Ph.D. theses

Author: CWIK Agnieszka
Supervisor: Dr. HELL Zoltán
associate professor
1. Introduction
Nowadays an important target in the preparative organic chemistry is the development of new reagents and catalysts which are more active, and selective than the traditional ones, easily handleable and reusable. These bases are environmentally-friendly materials. At the end of the reaction the catalyst can be recovered by simple filtration, there is no need for neutralization, so the salt- or base contamination of the wastewaters decreases and other corrosive factors do not appear. In addition, the filtered catalysts are usually reusable. They are cheap because of their natural source (partly modified to obtain an appropriate activity in the organic reactions) and non-toxic. We can achieve high activity and selectivity using them under relatively mild reaction conditions. Finally, because of their cavernous structure in some reactions a significant regio- or stereoselectivity could be obtained.

An important group of anionic clays is the layered double hydroxides. Originated from the best-known representative of this group, the hydrotalcite, they are often called hydrotalcit-type materials or simply hydrotalcites. They are generally used as polymer (PVC) stabilizing agents, as chloride ion trap, as well as anion exchangers, e.g. in water purifying technologies. Their structures closely resemble to the structure of brucite \([\text{Mg(OH)}_2]\): magnesium is octahedrally surrounded by six hydroxid ions. In the hydrotalcites some divalent cations are replaced by trivalent cations resulting in positively charged layers. Charge-balancing anions and water molecules are situated in
the interlayer space. The octahedral share edges to form an infinite sheet. The sheets are carefully stacked on top of each other and held together by hydrogen bonds (Figure 1).

![Figure 1. The structure of hydrotalcite](image)

The nature and ratio of the cations, as well as the different thermal pretreatments strongly influence the basicity and this way the catalytic activity of the hydrotalcites.

My research work was performed at Budapest University of Technology and Economics (BME), Department of Organic Chemical Technology. In the framework of the research project, my work was the examination of the applicability of mineral-based solid base catalysts (mainly hydrotalcite bases) in organic syntheses.

2. **Novel synthetic results**

2.1 I have found, that intramolecular cyclization of malonic acid allylic esters into bicyclic cyclopropane carboxylic acid lactones can be performed with non-activated of Mg:Al 3:1 hydrotalcite instead of potassium carbonate. The diastereoselectivity of the reaction was changed in the absence of phase transfer catalyst. The extent of this increase depended on the size of the R
substituent, a considerable effect was observed in the case of hydrogen, while this effect was smaller in the case of methyl or phenyl groups.

Without phase transfer catalyst the reaction could occur between the layers of the hydrotalcite, where the formation of the *exo* isomer is more favorable because of steric factors. The biggest change was observed in the case of the smallest substituent – hydrogen.

2.2 I have studied the reaction of ethyl nitroacetate with olefines in the presence of Mg:Al 3:1 hydrotalcite and other bases and I found, that instead of the expected cyclopropane carboxylic acid derivatives 4,5-dihydroisoxazolecarboxylic acid esters were formed.
Other bases such as KF/αAl₂O₃, pyridine, DBU, gave no product. When iodine was omitted from the reaction mixture no reaction occurred either. Replacing rehydrated Mg:Al 3:1 hydrotalcite by potassium carbonate under the same reaction conditions, the mixture of ethyl 5-butyl-4,5-dihydro-3-isoxazolcarboxylate and diethyl 1,2-dinitro-ethane-1,2-dicarboxylate was obtained. Examining the mechanism of the reaction we established that in contrast to the methods described in the literature, this new reaction was not a dipolar cycloaddition, but rather a radical process via an iodoester intermediate similar to the formation of cyclopropane carboxylic acid derivatives. The absence of the cyclopropane as product could be explained by O-alkylation of the aci-form of nitronate anione instead of the carbon atom of the active methylene group.

2.3 I have developed the synthesis of oxazolidin-2-one derivatives starting from carbamates in the presence of rehydrated Mg:Al 3:1 hydrotalcite in excellent yield (Y: 83-96%).
Based on the kinetic investigations of the cyclization the reaction can be used to the qualification of the hydrotalcite samples prepared.

2.4 I have worked out the synthesis of 4-hydroxy-arylpiperidine derivatives from bis-Mannich bases using non-activated Mg:Al 2:1 hydrotalcite. During the cyclisation only one diastereoisomer was formed, because of steric hindrance and the possibility of an hydrogen-bond formation between the carbonyl oxygen and the hydrogen of the hydroxyl group.

We have firstly published the use of the commercially available Mg:Al 2:1 hydrotalcite as catalyst in organic reactions in the literature.

2.5 During the investigation of the Henry-reaction (nitroaldol-addition) I have found, that that non-activated Mg:Al 2:1 hydrotalcite was a highly efficient basic catalyst for the preparation of the desired 2-nitroalcohols at room temperature. No the products of any competitive reactions such as aldol condensation, Cannizzaro-reaction, or the dehidration of 2-nitroalcohols were
observed. Increasing the temperature to 100 °C, in nitromethane, I observed the formation of mixture of 2-nitroalcohols and the well-known 1,3-dinitropropane derivatives, too.

We supposed a new mechanism for the formation of the 1,3-dinitro-compounds. Since nitromethane has a tautomeric aci-form this could protonate the Henry-product. This protonation would be followed by the loss of water and the cation thus formed would be attacked by the anion of nitromethane. The leaving of the water molecule and the attack of the anion could be occurred at the same time, in the $\text{S}_{\text{N}}^2$ reaction.

In the reaction of nitroethane and aromatic aldehydes with hydrotalcite I observed a significant difference in the threo/erythro diastereoselectivity compared with the data reported in the literature, which can be explained with the lamellar structure of the catalyst.
2.6 We have developed a new, heterogeneous, reusable Pd/MgLa mixed oxide catalyst, and we explored its catalytic properties toward different carbon-carbon coupling reactions. The Pd\textsuperscript{II}/MgLa mixed oxide was prepared by ion exchange, using an aqueous solution of Na\textsubscript{2}PdCl\textsubscript{4}. Using this procedure, highly dispersed chloropalladate anions are fixed at the surface of the support. The Pd\textsuperscript{0}/MgLa mixed oxide catalyst was obtained by the reduction of the Pd\textsuperscript{II}/MgLa with hydrazine hydrate.

We used this catalyst successfully in the Heck, Sonogashira, and Suzuki reactions. Aryl iodides gave excellent yields while moderate to good yields were obtained with the less active aryl bromides or chlorides. As expected, better results were obtained in the presence of activated aryl bromides and chlorides such as 4-bromoacetophenon, 4-chloroacetophenon, or 4-chlorobenzaldehyde. In the Sonogashira reaction there was no need for the copper cocatalyst.

The leaching of the palladium was very small, the reactions were performed under air atmosphere. The palladium content of the filtered solid was determined by ICP OES. The difference in Pd content between the fresh and used catalyst was up to 4%. The catalyst can be recovered by simple filtration and reused without significant loss of activity, which diminishes the cost of the process and the palladium contamination of the products.
3. Published articles on the subject of the dissertation

- Z. Finta, Z. Hell, D. Balán, A. Cwik, S. Kemény, F. Figueras

- A. Cwik, A. Fuchs, Z. Hell, J-M. Clacens

- A. Cwik, A. Fuchs, Z. Hell, J-M. Clacens

- A. Cwik, A. Fuchs, Z. Hell, I. Bőjtös, D. Halmai, P. Bombicz

- A. Cwik, Z. Hell, A. Fuchs, D. Halmai

Papers submitted

- A. Cwik, Z. Hell, F. Figueras
  Pd/MgLa mixed oxide catalyst in the Heck reaction: *Adv. Synth. Cat.*

- A. Cwik, Z. Hell, F. Figueras

**Other publications**

- **Z. Hell, A. Cwik, Z. Finta, Z. Horváth**

- **Z. Finta, Z. Hell, A. Cwik, L. Tőke**

- **A. Cwik, Z. Hell, A. Hegedüs, Z. Finta, Z. Horváth**

- **A. Hegedüs, A. Cwik, Z. Hell, Z. Horváth, Á. Esek, M. Uzsoki**

**Other presentations**

- **Z. Hell, S. Békássy, B. Ágai, K. Biró, A. Cwik, J. Farkas, Z. Finta, Z. Horváth**
  Application of Solid Acids and Bases in Fine Chemistry for Cleaner Processes

  Solid acid and base catalysts for cleaner fine chemical processes

  Szilárd bázisok és savak reaktivitásának vizsgálata szerves szintézisekben

- **Cwik A., Hell, Z., Fuchs A., Figueras, F.**
  Heterogén fázisú reakciók vizsgálata