Thesis of Ph.D. dissertation

Synthesis and application of new phase labelled catalyst

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The CBS catalyst **1 a, b** is an important molecule for the industry (Figure 1). As a first step, using "light-fluoros" technique we managed to derivatize the CBS catalyst in an Ullmann coupling (**2**) (Figure 2.). This way it became phase marked. The catalyst was then successfully used in asymmetric reduction of ketones. The phase labelling made possible the use of catalytic reactions in homogeneous phase. The enantioselectivity of these reactions were practically the same as for the original, non-derivatized CBS catalyst. The derivatized catalyst was recovered using fluoros solid phase extraction (Figure 3.). An important catalyst separation and recovery problem was solved by utilizing a fluoros technique.

The CBS catalyst

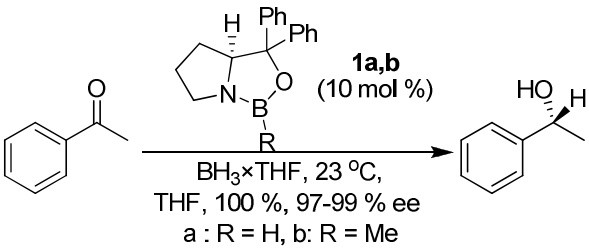

Figure 1.

The "light fluoros" CBS catalyst

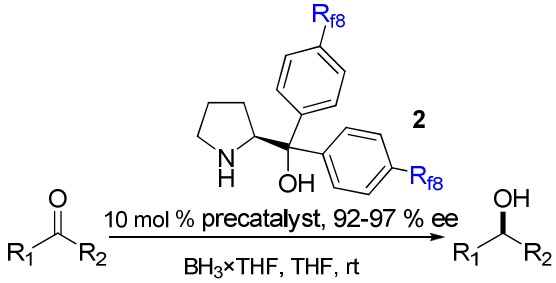

Figure 2.

Fluorous solid phase extraction

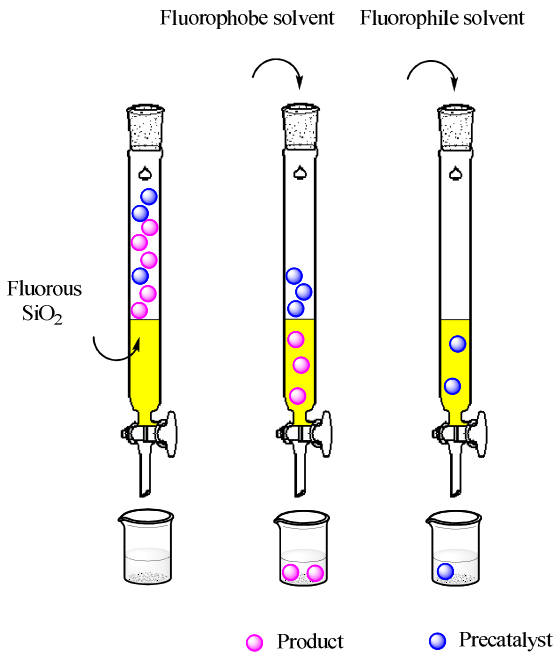

Figure 3.

In the past few years there were several publications detailing the bioaccumulation problem of long chain perfluoroalkyl molecules. They have been found in indoor air,

outdoor air, soil, ground water, surface waters and even at 1000 m depth in the Pacific Ocean. Perfluorinated compounds are widely distributed in wildlife. PFOS has been detected in blood and liver samples from various species of aquatic animals (seal, otter, sea lion, dolphin, polar bear, mink), birds, fish and amphibians.

Bioaccumulation in the animals

Figure 4.

This prompted us to try to radically reduce the chain length of the phase marker groups usually used in fluoros chemistry. Also we wanted to use hydrophobic, fluoros structural elements that are biodegradable. The trifluoromethyl group is used by drug manufacturers for over 10 years to increase lipofilicity. It satisfies the proposed criteria, thus we begun to study its usability as a phase marker moiety. The significant decrease of the size of the "phase marker" group required us to further develop the previously used fluoros separation methods (solvents, adsorbents). We recognized that the key element for a successful separation of the products from the trifluoromethyl substituted catalyst is tuning the composition of the used polar solvent, by addition of water. After optimization of the used catalysts and the solvent composition, we managed the easy separation of **3** "phase marked" CBS catalysts from the products, and the catalyst recovery.

New phase labelled precatalyst

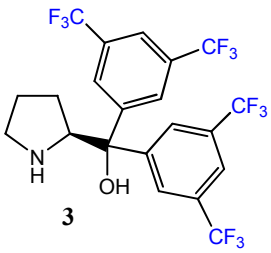

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Figure 5.

For catalyst recovery we developed solid phase and liquid-liquid extraction methods (Figure 6.) that use cheap solvents like water, methanol, acetonitrile or dimethylformamide, which are usually used in the industry.

Separation with liquid-liquid extraction without fluorous solvents

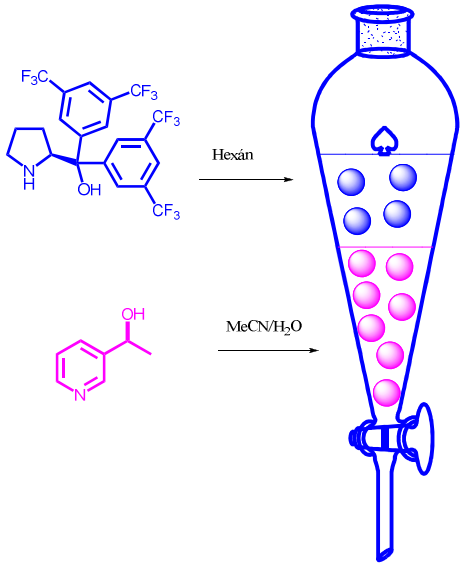


Figure 6.

To our best knowledge, we were the first to utilize corundum as sorbent for solid phase extraction. Lately, to reduce the quantity of used solvents, we developed a continuous operation U-tube extractor, with a methanol-water liquid membrane (Figure 7).

Continuous U-tube extractor with a methanol-water liquid membrane

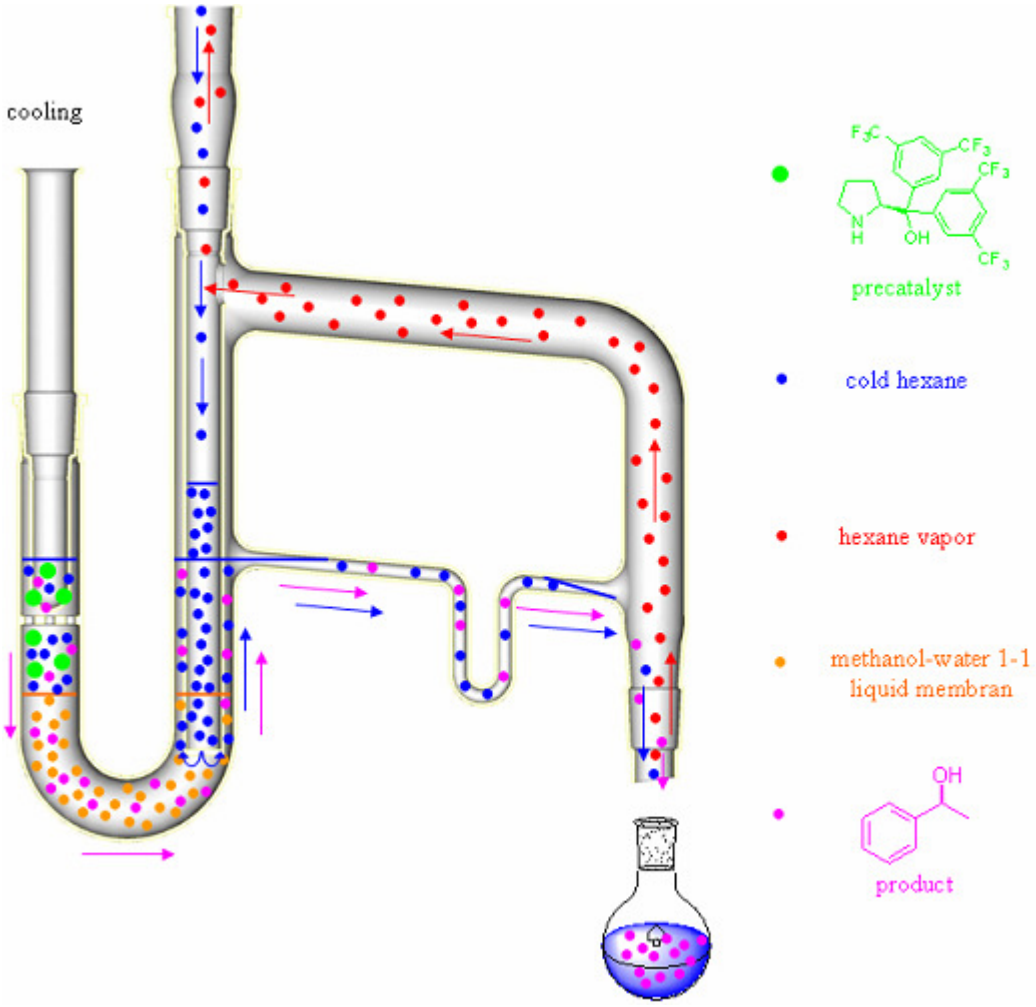


Figure 7.

Based on this work, we submitted two patents, both having been accepted. (P0700486, Procedure for immobilization of phase labelled diphenyl prolin catalysts, P0700490 Novel extraction equiqments)

Next we tested the usability of the developed method. Therefore we synthesized **4** triphenylphosfins substituted by trifluoromethyl groups and its **5** Pd(0) complex (Figure 8.).

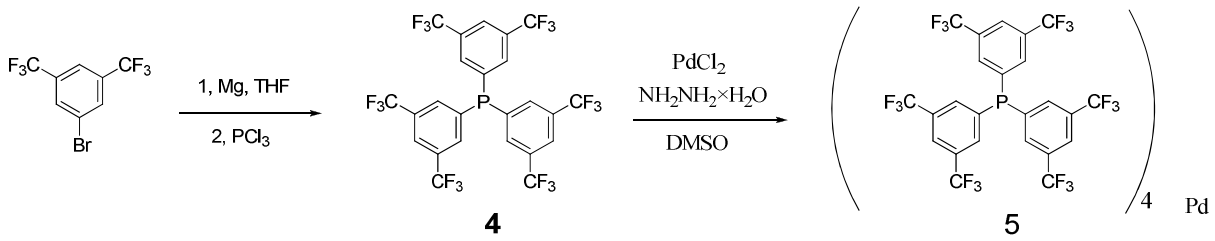


Figure 8. Synthesis of the phase labelled Pd-tetrakistriphenilphosfine

These complexes were then successfully used in Suzuki reaction, as catalyst. A very important feature of the catalyst is its high stability towards water and oxygen (Figure 9).

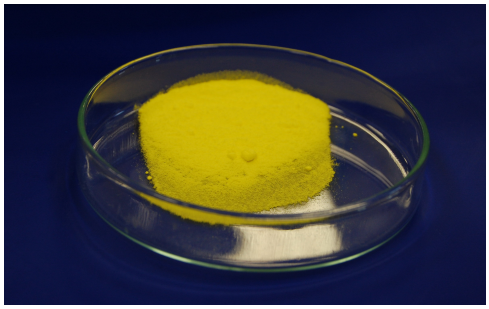
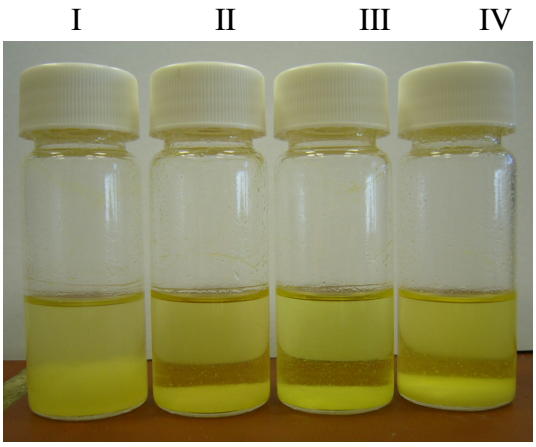


Figure 9. Fluorous Pd(0) complex

The catalyst is quite stable under the used reaction conditions. The reactions were done at 110°C. The yellow color of the catalyst was always visible, without the appearance of Pd's black color.



The synthethised products

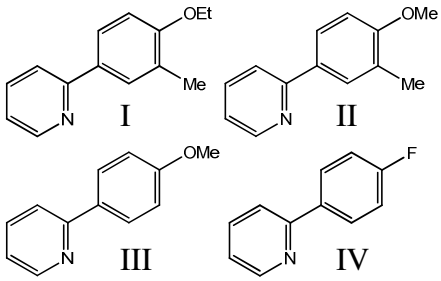


Figure 10. The reaction mixture after 1 hour at 110 °C

After optimizing the reaction conditions, the productivity of the biaryl crosscoupling products was high. For product purification several methods were developed. These enable us to reduce the Pd content of the products under the 1 ppm limit.

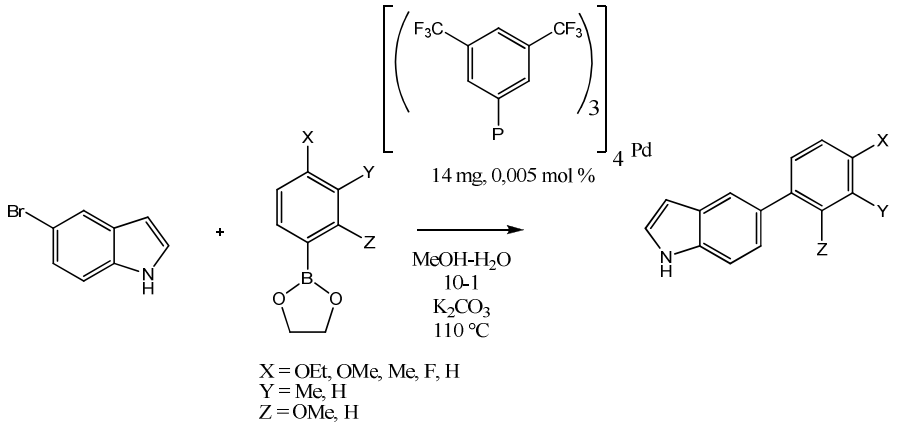
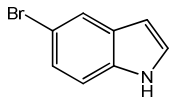
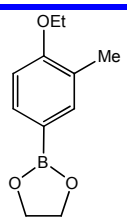
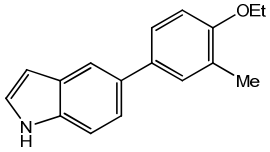
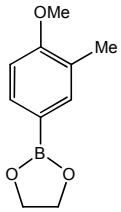
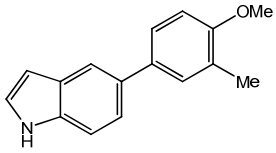
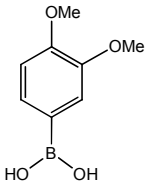
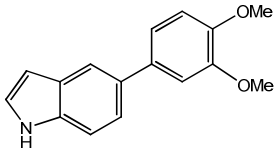
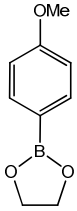
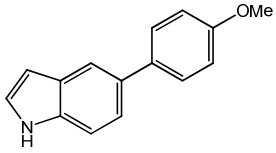
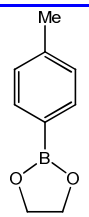
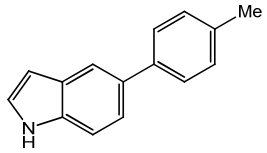
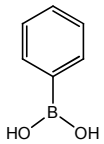
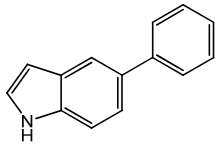
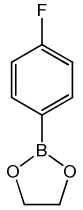
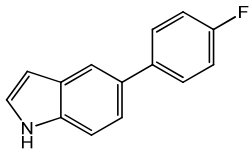


Figure 11. Synthesis of several indole derivatives

	t (h)	T (°C)	catalyst mg/mol %	reagents		yield %
1	1	110	14/0,25			93
2	1	110	14/0,25			90
3	1	110	14/0,25			94
4	1	110	14/0,25			87

5	1	110	14/0,25			92
6	1	110	14/0,25			84
7	1	110	14/0,25			77

List of publications

Patents:

P0700486 Procedure for immobilization of phase labelled diphenyl prolin catalysts
P0700490 Novel extraction equiqments

Publications:

Dalicsek Zoltán, Pollreisz Ferenc, Gömöry Ágnes, Soós Tibor
Recoverable fluorous CBS methodology for asymmetric reduction of ketones ORGANIC LETTERS, 2005, 7; 3243

Dalicsek Zoltán, Soós Tibor
Recoverable fluorous CBS methodology for asymmetric reduction of ketones.
LETTERS IN ORGANIC CHEMISTRY, 2006, 3, 81

Dalicsek Zoltán, Pollreisz Ferenc, Soós Tibor
Efficient Separation of a Trifluoromethyl Substituted Organocatalyst: Just Add Water
Chemical Communication

Posters:

1. Synthesis of fluorous oxazaborolidine catalyst and applications in enantioselective catalytic reduction.
2. Recoverable fluorous CBS methodology for asymmetric reduction of ketones
3. Goldilock's effect in a phase labelling: superlight fluorous methodology

Konferencia részvételek:

1. 10th Blue Danube Symposium, Bécs, 2003.szeptember 3-6
2. XXIst European Colloquium on Heterocyclic Chemistry, Sopron, 2004. szeptember 12-15

3. Green Chemistry: Development of Sustainable Processes, Rostock, 2005. március 30- április 1
4. Vegyészkonferencia, Hajdúszoboszló, 2005. június 28-30
5. Frontiers in Catalysis Symposium, Visegrád, 2005. szeptember 8-10
6. Ischia Advanced School of Organic Chemistry, IASOC 2006. szeptember 16-21
7. Vegyészkonferencia, Hajdúszoboszló, 2008. június 19-21
8. Blue Danube Symposium on Heterocyclic Chemistry, Tihany, 2007. június 10-13.
8. Ischia Advanced School of Organic Chemistry, IASOC 2008. szeptember 27-október 2
9. Heterociklusos Kémiai Munkabizottság, Balatonszemes, 2003-2008