Development and application of copper on iron catalysts and imidazolylsulfonate-based benzyne precursors for the synthesis of heterocycles

Theses of the PhD dissertation

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1. Introduction, Objectives

Copper-catalyzed reactions

The application of copper in organic chemistry began more than a hundred years ago. In the beginning of the twentieth century several carbon-carbon and carbon-heteroatom bond formating reactions were carried out in the presence of copper-catalysts. These reactions required harsh conditions, and the products often were afforded only in low yields. Since the 1980s, the spread of cross-coupling reactions and the application of different types of copper-catalysts and ligands have caused the easement of reaction conditions, so more effective catalytic procedures have been developed.[1] Nowadays besides the application of copper-complexes and salts, heterogeneous copper catalysts are often used, which are in the form of Cu(I) complexes on carrier or copper nanoparticles stabilized in solution or absorbed on carrier.

During my PhD work my aim was the synthesis of a new type of two-compound heterogeneous copper on iron catalyst and the applicability of the catalyst in C-C and C-heteroatom bond formation reactions and cycloaddition reactions.

Copper-catalyzed C-S bond formation

With the spread of cross-coupling reactions, C-S couplings have been the subject of renewed attention. During the 1980s, Suzuki and coworkers showed first the applicability of copper in the coupling reaction of aryl iodides and aromatic thiols in mild reaction media.[2] In the last decade several copper-catalyzed transformations were developed in which diaryl and aryl-alkyl sulfides were formed with the help of multiple bonded N and O ligands in mild reaction conditions.[3] Besides the homogeneous catalyst-systems, heterogeneous copper-catalysts have also been successfully applied in the synthesis of aromatic sulfides with the use of different copper and immobilized CuO nanoparticles. In the formation of C-S bonds in transition metal-catalyzed reactions, a problem arises in the form of a disulfide side product that is generated by thiol oxidation. Using a reductive reaction media eliminates the undesirable disulfide side product; in fact, disulfides can be used as a starting material and

[1] Ley, S. V.; Thomas, A. W. *Angew. Chem. Int. Ed.* **2003**, *42*, 5400.
[2] Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* **1980**, 1363.
[3] Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596.

reduced to thiols in situ using reducting conditions. A reductive reaction medium can be ensured by using solid magnesium[4], sodium ascorbate[5] or iron powder.[6]

Copper-catalyzed azide-alkyne cycloaddition (CuAAC)

In the beginning of 2000, Sharpless[7] and Meldal[8] independently discovered at the same time that the azide-alkyne 1,3-dipolar cycloaddition can be carried out at room temperature in the presence of Cu(I) ions and 1,4-substituted triazole is produced selectively.

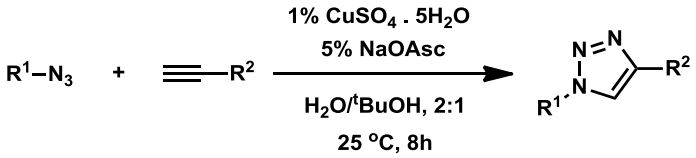

Figure 1: CuAAC reaction

The copper-catalyzed cycloaddition provided fast, effective and selective synthesis of triazoles in mild reaction conditions, which resulted in the wide application of the reaction. The copper catalysts needed for the transformation are usually in the form of copper(I)-halides (mainly CuI) or they are generated in situ by the reduction of copper(II) salts using reducing agents and thereby forming the active component. In the last decades numerous researcher have been working on the development of more effective catalyst-systems, applying various N-containing ligands and special copper complexes. Along with the homogeneous copper-catalyzed transformations, several heterogeneous copper-catalyzed cycloadditions are known in literature, in which copper-catalysts on carriers and copper nanoparticles served as catalysts.

Synthesis of enamines and pyrazoles

Cycloaddition reactions of nitrile oxides are widely used for the synthesis of various heterocycles; isoxazolines and isoxazoles are formed with help of olefins and acetylenes respectively. Isoxazoles are important building blocks in synthetic chemistry. Numerous biologically active species contain isoxazole unit, though the utilization of them in agricultural chemistry, dye industry and electronics is significant as well. Because of the weak N-O bond in the five-membered heterocycle, isoxazoles are easily transformed, e.g. opening the ring can be used for preparing further heterocycles. The ring-opening reaction of

[4] Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, *69*, 915.
[5] Martinek, M.; Korf, M.; Srogl, J. *Chem. Commun.*, **2010**, *46*, 4387.
[6] Li, Y.; Wang, H.; Jiang, L.; Chen, T. *Eur. J. Org. Chem.* **2010,** *11*, 2324.
[7] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**,*41*, 2596.
[8] Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.

isoxazoles has been known for a hundred years. From the middle of the twentieth century substituted enamines were formed with hydrogenation using Raney Ni, palladium on charcoal or platinum catalysts. From the eighties, N-O cleavage was carried out through iron and molybdenum complexes,[9] samarium iodide,[10] Fe(II) complexes[11] and $FeCl_2$.[12] Pyrazoles can be prepared from the respective isoxazoles. The pyrazole ring forms during the ring opening, because the nascent enaminone condensates with hydrazone.

Application of TMS-phenyltriflate precursor in organic chemical transformations

Dehydrobenzene is a strained, triple-bond containing cyclic molecule, which can formally be derived from benzene by the elimination of two hydrogen atoms. Because of its strained structure, dehydrobenzene is very reactive even at low temperatures, therefore it is necessary to prepare it in situ from various benzyne precursors. Several methods were developed for generating benzynes, among them Kobayashi's method is the most significant one.[13] The development of *o*-TMS triflate precursor was an important milestone in benzyne chemistry. The generation of dehydrobenzene was performed in a straightforward manner in a fluoride-induced reaction under mild reaction conditions.

Because of their high reactivity, the application of arynes is widespread. A lot of examples can be found in literatures for pericyclic reactions in which TMS-aryltriflate precursor is used.[14,15,16] It reacts with dienes in Diels-Alder reaction, with olefins in [2+2] cycloaddition and with dipoles in 1,3 dipolar cycloaddition producing different carbo and heterocycles. TMS-aryltriflate precursor is often applied in various multiple component and transition metal catalyzed reactions as well.

Because of their high reactivity, triflates have been readily used in transition metal catalyzed reactions since the eighties.[17] Albeit high reactivity leads to the instability of the triflates, as they have a short storage life and the triflating agents used for their preparation are expensive and hard to handle. Apart from these it is important to mention that the formation of sulfonic acids from the leaving sulfonates – triflates, mesylates, tosylates – are potentially genotoxic, which is a significant drawback in industrial application.

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[9] Nitta, M.; Kobayashi, T. *Tetrahedron Lett.*, **1982**, *23*, 3925.
[10] Natale, N. R. *Tetrahedron Lett.*, **1982**, *23*, 5009.
[11] Kijima, M.; Nambu, Y.; Endo, T. *J. Org. Chem.*, **1985**, *50*, 1140.
[12] Auricchio, S.; Bini, A.; Pastormerlo, E.; Truscello, A. M. *Tetrahedron*, **1997**, *53*, 10911.
[13] Himeshima, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.
[14] Pellissier, H.; Santelli, M. *Tetrahedron*, **2003**, 701.
[15] Bhunia, A.; Yetra, R. S.; Biju, T. A. *Chem. Soc. Rev.* **2012**, *41*, 3140.
[16] Dubrovskiy, A. V.; Markina, N. A.; Larock, R. C. *Org. Biomol. Chem.* **2013**, *11*, 191.
[17] Ritter, K.; *Synthesis.* **1993**, 735.

To circumvent these problems Albaneze-Walker and coworkers introduced imidazolylsulfonates as a triflate alternative for Suzuki coupling (Figure 2).[18]

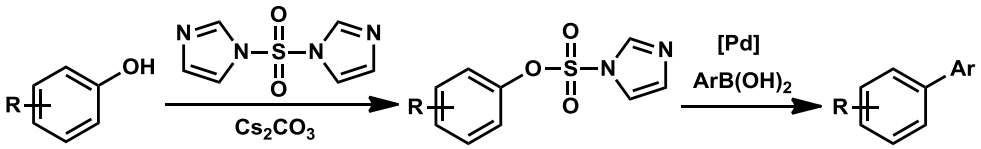

Figure 2: Synthesis of aryl imidazolates and their application in Suzuki reaction.

The stable imidazolylsulfonates are prepared from sulfonyldiimidazoles (SDI) and phenol-derivatives and according to investigations the reactivity of imidazoyl group in cross-coupling reactions is almost similar to triflates, in addition the formed imidazole-sulfonic acid hydrolyzes to produce imidazole and sulfuric acid, which has a beneficial industrial applicability compared with triflates.

Results

During our work we have developed and prepared a simple and easily accessible active copper (0) catalyst. Using iron as carrier we have prepared an electrochemically precipitated copper catalyst on the surface of the iron. Thanks to the ferromagnetic property of the iron, with the help of an outer magnetic field the catalyst can be easily separated after the usage and it is recyclable. In addition, it ensures a reductive reacting media, thereby it stabilizes the copper particles and reduces the oxidized form of the copper. The structure and surface of the catalyst were examined by scanning electron microscope and the exact quantity of the copper was measured by atom absorption measurements.

Formation of C-S bond through the application of copper on iron catalyst

The first application of the developed catalyst was the formation of carbon-sulfur bonds in the thiolation reaction of aromatic halides.[19] The iron supported copper catalyst was found to be an effective method for the preparation of aromatic sulfides. With the help of a model reaction of iodobenzene and thiophenol we have optimized the reaction conditions and determined the quantity of the Cu/Fe catalyst needed for the reaction, as well as the optimal copper:iron ratio (5 mol% copper (5 w/w%)Cu/Fe). Next we examined the base and solvent effect and the results showed that inorganic bases and polar media are preferable for the reaction, and the most suitable solvent/base pair was found to be DMA/K_2CO_3 for the effective formation of the carbon-sulfer bond. Applying the optimized reaction media we have

[18] Albaneze-Walker, J.; Raju, R.; Vance, A. J.; Goodman, J. A.; Reeder, R. M.; Liao, J.; Maust, T. M.; Irish, A. P.; Espino, P.; Andrews, R. D. *Org. Lett.* **2009**, *11*, 1463.
[19] Kovács, Sz.; Novák, Z. *Org. Biomol. Chem.* **2011**, *9*, 711.

observed the rapid oxidation of disulfide from thiol at the beginning of the reaction, but after the appropriate period of time the intermediate was completely consumed via reductive cleavage and subsequent coupling. The oxidation is supposedly caused by the traces of Fe(II) ions on the catalyst, which have been confirmed by ^{19}F-NMR measurements.

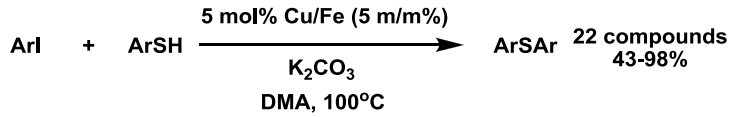

Figure 3: Preparation of diaryl sulfides using Cu/Fe catalyst

To explore the scope of the reaction, we performed the coupling reactions of structurally and electronically diverse thiols and aryl iodides, as well as electron deficient bromides and chlorides. A total of 22 thioethers were prepared (Figure 3).

Synthesis of triazoles utilizing heterogeneous Cu/Fe catalyst

The applicability of the catalyst after the successful formation of C-S bond was examined in various dipolar cycloaddition reactions.[20] Phenylacetylene and benzyl azide were selected as the reactants for the model reaction and optimizing the reaction conditions, during the course of which we have determined the amount of the catalyst required (5 mol% copper-content (5w/w%)Cu/Fe), the temperature (30 °C) and the suitable solvent (DCM). Under the developed conditions we synthesized 19 triazole derivatives with good yields (61-98%, Figure 4) using several azides and acetylenes.

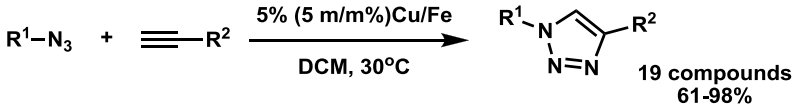

Figure 4: Azide-alkyne cycloaddition in the presence of Cu/Fe catalyst

Examining the reaction rate in time, we have shown that the reaction was completed in a short time after an induction period. We have proved that the nascent product influences the reaction rate as a ligand and that the transformation of the reaction happens in homogeneous catalytic reaction media supposedly through forming an active copper complex. We showed that the Cu/Fe catalyst is reusable in 15 consecutive reactions without a reduction rate in catalytic activity. We have demonstrated that the iron serves not only for the easy separation of the catalyst but acts as a redox scavenger and reduces the copper contamination of the product, which is now significantly lower than the triazoles synthesized under homogeneous catalytic conditions.

[20] Kovács, Sz.; Zih-Perényi, K.; Révész, Á.; Novák, Z. *Synthesis*, **2012**, *44*, 3722.

Preparation of pyrazoles and enamines using Cu/Fe catalyst

We have developed the synthesis of *β*-enaminones from hydroximoyl chlorides and acetylenes in a cycloaddition reaction that procedes through an isoxazole intermediate with the aid of copper on iron catalyst. During the optimization, we showed that a stochiometric amount of iron is necessary to perform the reductive ring opening, while copper accelerates the reaction through the promotion of cycloaddition. Mechanistic studies showed that HCl was formed in the cycloaddition reaction during the formation of nitrile oxide; the HCl reacts with the iron carrier of the Cu/Fe catalyst and promotes the opening of the isoxazole ring. Under the developed conditions (5 mol% (5w/w% Cu/Fe), DMF, 100 °C) we synthesized 9 *β*-enaminones with 36-71% yields using various aromatic chlorooximes and aromatic, aliphatic and heteroaromatic acetylenes.

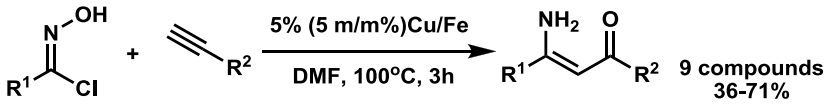

Figure 5: Synthesis of enaminones

The previously formed enaminones were reacted with in situ generated hydrazine under the same optimized conditions, generating a one pot synthesis for the preparation of 3,5-disubstituted pyrazoles. We have prepared 15 pyrazole products giving 44-74% yields using diverse aromatic and heteroaromatic chlorooximes and aromatic, aliphatic and heteroaromatic acetylenes.

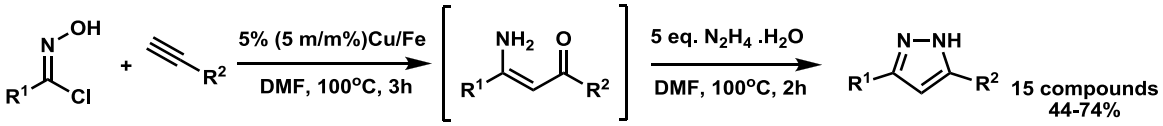

Figure 6: One pot synthesis of pyrazoles

Design and application of imidazolylsulfonate-based benzyne precursors in organic chemical syntheses

In the second part of my research, I have developed and studied the applicability of the new imidazolylsulfonate-based benyzne precursors.[21] Using the beneficial properties of imidazylate group I have designed a new *ortho*-TMS imidazolylsulfonate precursor and I have developed a convenient preparation of the precursors from 2-bromophenols in a one pot synthesis. Applying the developed method, I have prepared mono and disubstituted precursors with 28-77% yield in 10 mmol quantities using several methyl and fluoro substituents. In

[21] Kovács, Sz.; Csincsi, Á. I.; Nagy, T. Zs.; Boros, S.; Timári, G.; Novák, Z. *Org. Lett.* **2012**, *14*, 2022.

addition, starting from 2-hydroxy-3-trimethylsilylpiridine I have synthesized a precursor with 45% yield in an analogous way[18], which contains a pyridine ring.

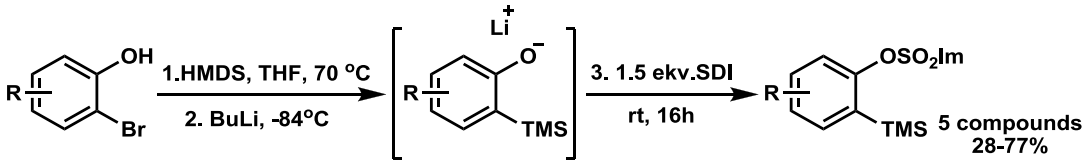

Figure 7: One pot synthesis of imidazolylsulfonate precursor

We have studied the applicability of the precursors on reactions analogous to those carried out by diverse triflate precursors. First, we performed several Diels-Alder reactions with dienes such as furans and N-Boc-pyrrole, preparing 5 different bridged heterocycles with good yield (50-73%, Figure 8).

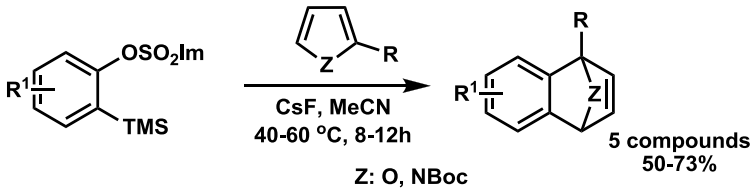

Figure 8: The application of imidazolylsulfonate precursor in Diels-Alder reactions

In the next step, we examined the newly developed precursor in a 1,3-dipolar cycloaddition reaction. We reacted the synthesized benzyne precursors with various aromatic and aliphatic azides, preparing 10 benztriazoles with equally good yields (17-76%, Figure 9) as in literature[22].

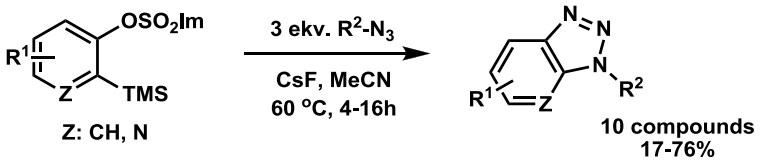

Figure 9: Synthesis of benztriazoles with imidazilate precursors

Applying the conditions of Shi and Larock[23] we had the imidazolylsulfonate precursor reacted with tosyl-hydrazones and prepared 6 indazoles bearing substituents on the phenyl ring in position 3 with a yield of 51-71% (Figure 10).

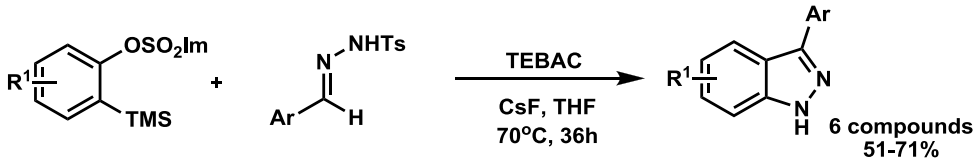

Figure 10: Preparation of indazoles in 1,3-dipolar cycloaddition using arynes

[22] Shi, F.; Waldo, J. P.; Chen, Y.; Larock, R. C. *Org. Lett*. **2008**, *10*, 2409.
[23] Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340.

Following the successful cycloaddition reactions, we have examined the imidazolylsulfonate precursor in an insertion reaction as well. As described by Stoltz and Tambar, in the presence of *β*-ketoesters *o*-acyl alkylation of the aromatic ring takes place when benzyne is generated from *o*-silyl-aryltriflates.[24] Applying analogous conditions we prepared 4 *o*-acylalkylated compounds with 45-90% yields using different ketoesters.

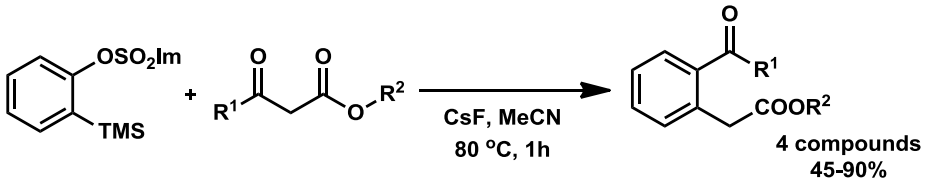

Figure 11: Insertion reaction of *β*-ketoesters with imidazolylsulfonate precursor

Comparing the precursor developed in this work with the widely used 2-trimethylsilyl-phenyltriflate precursor we have showed that the synthesis of the imidazolylsulfonate precursor is more economical and more convenient regarding safety aspects as well. The reactivity of the precursors was studied by cyloaddition reactions with azides and we have demonstrated that the imidazolylsulfonate-based precursor shows similar reactivity as the triflate derivative.

2. Publications giving the basis of the dissertation

1) Kovács, Sz.; Novák, Z.; Oxidoreductive coupling of thiols with aryl halides catalyzed by copper on iron, *Org. Biomol. Chem.* **2011**, *9*, 711.
2) Kovács, Sz.; Zih-Perényi, K.; Révész, Á.; Novák, Z.: Copper on iron: Catalyst and scavenger for azide-alk*yne cycloaddition*, *Synthesis*, **2012**, *44*, 3722.
3) Kovács, Sz.; Csincsi, Á. I.; Nagy, T. Zs.; Boros, S.; Timári, G.; Novák, Z.: Design and Application of New Imidazolylsulfonate-Based Benzyne Precursor: An Efficient Triflate Alternative, *Org. Lett.* **2012**, *14*, 2022.

3. Presentations and posters:

1) Szabolcs Kovács, Zoltán Novák: Réz-vas katalizátorok alkalmazása heterociklusok szintézisében és funkcionalizálásában, előadás, MTA Heterociklusos Kémiai Munkabizottság ülése, Balatonszemes, 2011.
2) Szabolcs Kovács, Zoltán Novák: The application of copper on iron magnetically reusable catalyst, poszter szekció, European Symposium on Organic Chemistry, Crete, 2011.
3) Szabolcs Kovács, Ádám I. Csincsi, Tibor Zs. Nagy, Sándor Boros, Géza Timári, Zoltán Novák: Új benzin-prekurzor kifejlesztése és alkalmazása heterociklusok szintézisében, előadás, MTA Heterociklusos és Elemorganikus Kémiai Munkabizottság ülése, Balatonszemes, 2012.
4) Szabolcs Kovács, Ádám I. Csincsi, Tibor Zs. Nagy, Sándor Boros, Géza Timári, Zoltán Novák: Design and Application of New Imidazolylsulfonate-Based Benzyne Precursor: An Efficient Triflate Alternative, poszter szekció, 4th EuCheMS Chemistry Congress, Prague, 2012.

[24] Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc*. **2005**, *127*, 5340.