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Development and Application of a Recyclable High-Load Magnetic Co/C Hybrid ROMP-Derived Benzenesulfonyl Chloride Reagent and Utility of Corresponding Analogues

Saqib Faisal,[†,‡] Qin Zang,[†,‡] Pradip K. Maity,[†,‡] Agnes Brandhofer,[†,‡,∥] Patrick C. Kearney,[§] Oliver Reiser,[∥] Robert N. Grass,[⊥] Diana Stoianova,[#] and Paul R. Hanson*[,†,‡]

[†]Department of Chemistry, University of Kansas, 1251 Wescoe Hall Drive, Lawrence, Kansas 66045-7582, United States

[‡]The University of Kansas Center for Chemical Methodologies and Library Development (KU-CMLD), 2034 Becker Drive, Delbert M. Shankel Structural Biology Center, Lawrence, Kansas 66047, United States

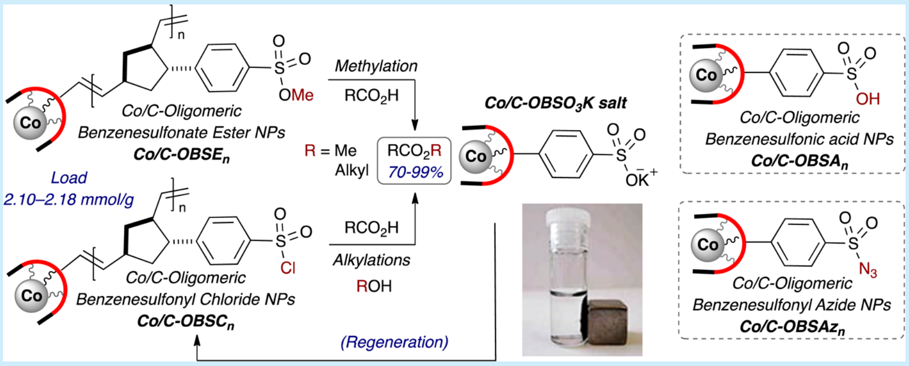
[§]HD Sciences, Kansas City, Missouri 66103, United States

[∥]Institute for Organic Chemistry, University of Regensburg, Universitatsstrasse 31, 93053 Regensburg, Germany

[⊥]Institute for Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 1-5/10, 8093 Zürich, Switzerland

[#]Materia, Inc., 60 North San Gabriel Boulevard, Pasadena, California 91107, United States

Ⓢ *Supporting Information*



ABSTRACT: The development and application of high-load, recyclable magnetic Co/C hybrid ROMP-derived benzenesulfonyl chloride and analogues is reported. The regeneration and utility of these reagents in the methylation/alkylation of various carboxylic acids is demonstrated via efficient retrieval of the magnetic reagent with a neodymium magnet. Additional reactions employing the analogue sulfonic acid and in situ generated magnetic benzenesulfonyl azide are also reported.

The growing demand for recyclable materials has resulted in an increasing need for the development of sustainable technologies in the production of chemical entities.[1] Recovery and recycling of expensive or toxic reagents in a more sustainable manner is an important area in minimizing environmental impact. Among many technologies being developed toward this goal, the use of magnetically supported reagents has emerged as a viable method of recovery due to their innate physical properties, including advantageous means of isolation and recyclability.[2] Despite ongoing developments for magnetic reagents and key advances in this area, noted limitations in load levels, physical properties (swelling, accessibility, etc.), ease of synthesis, and reuse are continued challenges to be met.

The synthesis of hybrid materials, which combine the properties of Co/C magnetic nanoparticles developed by Stark, Grass, and co-workers[3] with a high-load functionalized material,[3b−d] is a powerful means to address the limitations in the area of immobilized reagents. In this regard, pioneering work by Barrett,[4] Buchmeiser,[5] Bolm,[6] and others[7] has demonstrated ring-opening metathesis polymerization (ROMP)[8] as a viable technology for grafting oligomers onto a variety of surfaces. In this area, our group has reported ROMP-derived soluble, high-load, oligomeric reagents and scavengers through the use of norbornene-tagged (NB-tagged) monomers.[9] In addition, recent developments in our laboratories have demonstrated advancements in grafting high load oligomeric reagents and scavengers onto SiO_2[10] and magnetic Co/C surfaces[3,11] for application in facilitated synthesis and sequestration protocols. Our interest in this area has led to efforts aimed at the development of methylation/alkylation reactions using magnetic reagents.

Common methylating reagents, such as dimethyl sulfate, methyl iodide, and diazomethane, are extensively used in organic

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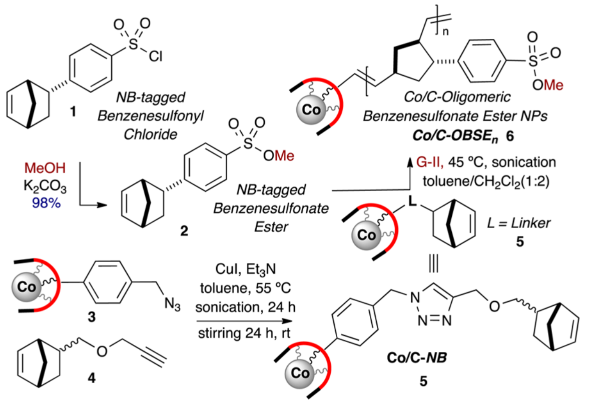
and medicinal chemistry but have undesirable physical characteristics that pose potential safety issues when used for routine synthesis, such as toxicity, carcinogenicity, and an explosive nature.[12] Alternative, safe, bench-stable, polymer-supported, and recyclable methylating or alkylating reagents represent a potentially more viable platform with enhanced safety/toxicity profiles for routine synthetic transformations.[13] In this regard, herein we report the first example of high-load magnetic Co/C-ROMP-derived oligomeric benzenesulfonate ester (Co/C-OBSE$_n$) and the in situ use of benzenesulfonyl chloride (Co/C-OBSC$_n$)/ROH as efficient methylating/alkylating reagents for various carboxylic acids.

To synthesize the magnetic version of oligomeric benzenesulfonate ester Co/C-OBSE$_n$, we first synthesized NB-tagged benzenesulfonyl chloride monomer **1** utilizing our previously reported procedure[14] (Scheme 1). The synthesis of Co/C-NB **5** is achieved by the utilization of a Cu(I)-catalyzed alkyne/azide cycloaddition reaction using commercially available Co/C-azide **3** and propargylated bicycle[2.2.1]hept-5-en-2-ylmethanol **4** (Scheme 1). This NB-tagged magnetic linker (Co/C-NB) **5** has been established as a suitable precursor for the surface-initiated ROMP of various NB-tagged monomers.[11]

Scheme 1. Magnetic Co/C Hybrid ROMP Benzenesulfonate Ester NPs (Co/C-OBSE$_n$)



The NB-tagged benzenesulfonate ester monomer **2** was synthesized by grinding NB-tagged sulfonyl chloride **1** in wet MeOH, which afforded compound **2** in excellent yield and high purity without the need to perform column chromatography (Scheme 1).[15] Subsequent surface-initiated ROMP[11] of NB-tagged sulfonate monomer **2** using the Grubbs second-generation catalyst [G-II, C848, (IMesH$_2$) (PCy$_3$) (Cl$_2$)-Ru = CHPh] afforded the desired ROMPgel grafted onto the surface of the Co/C nanobeads. More than 95% of monomer was incorporated into the hybrid material, resulting in magnetic NPs with a load of 2.10−2.18 mmol/g. To utilize this magnetic Co/C-OBSE$_n$, initial studies were focused on the methylation of simple carboxylic acid substrates. The reagent Co/C-OBSE$_n$ **6** was successfully utilized for methylation of various carboxylic acids **7a−e** (Figure 1), which afforded excellent yield (88−95%) and purity after retrieval of the spent magnetic reagent using a neodymium magnet and filtration through a Celite SPE to remove insoluble base.

Efforts were next focused on the synthesis of magnetic benzenesulfonyl chloride, Co/C-OBSC$_n$, which could subsequently be used for in situ direct alkylations of a carboxylic acid in the presence of alcohols without preparation/isolation of the sulfonate ester. In this regard, grafting of NB-tagged benzenesulfonyl chloride **1** was successfully achieved on a gram scale by using the aforementioned ROMP protocol, which afforded hybrid ROMP-derived magnetic benzenesulfonyl chloride NPs Co/C-OBSC$_n$ **8** (Scheme 2).

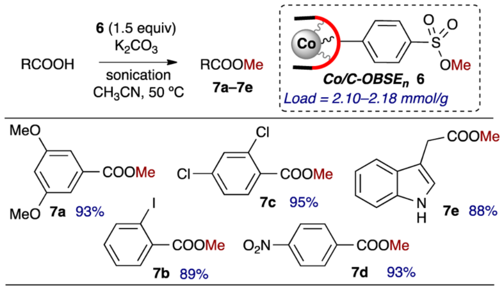
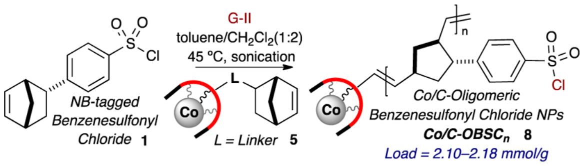


Figure 1. Methylation of various carboxylic acids utilizing magnetic Co/C-OBSE$_n$.

Scheme 2. Synthesis of Hybrid Magnetic Co/C-ROMP Benzenesulfonyl Chloride NPs Co/C-OBSC$_n$



Images of the hybrid material were next taken using transmission electron microscopy (TEM) to observe and evaluate the grafting of the corresponding NB-tagged monomers onto the surface of the Co/C-nanoparticles (Figure 2). The grafted ROMP polymer (light gray areas) is clearly attached around the Co/C NPs (dark area), and individual particles can be seen. The lack of large cohesive particles may indicate lack of cross-linking. This observation is substantiated by the fact that the experimental load values are similar to the theoretical loads, indicating that the majority of active sites were available and most likely not cross-linked.

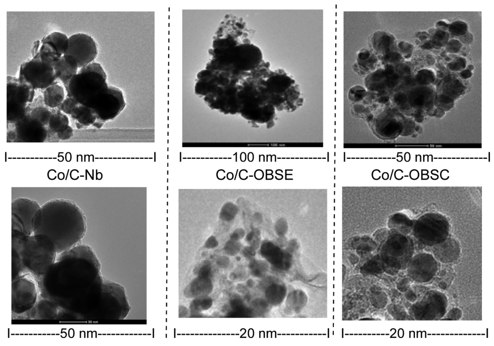
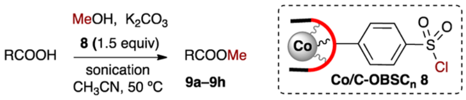
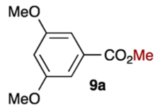
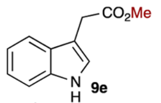
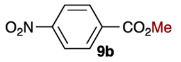
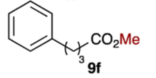
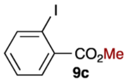
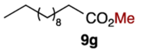
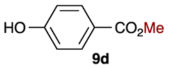
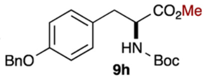


Figure 2. TEM Images of Co/C-NB, Co/C-OBSE$_n$, and Co/C-OBSC$_n$.

Direct methylations of carboxylic acids were successfully achieved via utilization of the magnetic reagent Co/C-OBSC$_n$ **8** in the presence of an excess of MeOH (6−10 equiv). Various simple aromatic and aliphatic carboxylic acids were subjected to methylation, which afforded the majority of products **9a−h** in excellent yields and purity (Table 1). In addition, chemoselective methylation of a carboxylic acid group was observed in the presence of a phenolic hydroxyl group (entry 4).

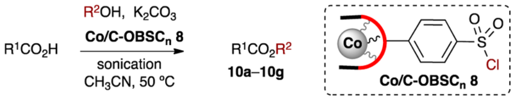
Table 1. Methylation of Various Carboxylic Acids Utilizing Magnetic Co/C-OBSC$_n$

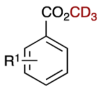
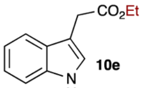
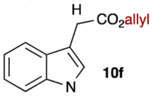
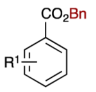
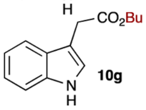


entry	product	yield(%)	entry	product	yield(%)
1	 **9a**	96	5	 **9e**	93
2	 **9b**	99	6	 **9f**	92
3	 **9c**	89	7	 **9g**	95
4	 **9d**	90	8	 **9h**	70

Considering the wide applications of esterification reactions,[16] we next directed our attention to further explore the scope of magnetic Co/C-OBSC$_n$ reagent for the alkylation of carboxylic acids with various alcohols. Toward this goal, reaction of carboxylic acids with deuterated MeOH was successfully achieved in <90% yield and purity (**10a** and **10b**, Table 2). In addition, alkylation in the presence of different alcohols afforded the desired alkylated ester (**10c**–**g**) in 72–82% yield. In all cases, the spent reagent was quantitatively retrieved by magnetic decantation of the reaction mixture.

Table 2. Alkylation of Carboxylic Acids Utilizing Magnetic (Co/C-OBSC$_n$)



R^{2}OH	product	yield(%)	R^{2}OH	product	yield(%)
CD$_3$OD	 R^1 = **10a**) 3,5-OMe **10b**) *p*-NO$_2$	93 95	EtOH	 **10e**	82
			Allyl-OH	 **10f**	78
BnOH	 R^1 = **10c**) 3,5-OMe **10d**) *p*-NO$_2$	72 75	*n*BuOH	 **10g**	80

Our next goal was to regenerate Co/C-OBSC$_n$ **8** from the corresponding magnetic NP sulfonic acid salts, Co/C-OBSA$_n$ **11**, being formed in the course of the reaction. To achieve this goal, the spent reagent was treated with $SOCl_2$ in toluene in the presence of a catalytic amount of DMF, which successfully afforded magnetic sulfonyl chloride NPs, Co/C-OBSC$_n$ **8** (Figure 3), without significant loss of magnetic material. Multiple esterifications/regenerations (up to 10×) were successfully achieved without any loss in performance using the same protocol. It was observed that the Co/C magnetic nanoparticles survived the acidic environment of the regeneration process, which has also been shown in a previous report.[17] It is also possible that the grafted ROMP gel provides additional protection of the core magnetic nanoparticles.

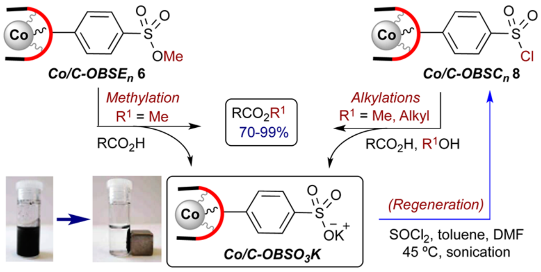
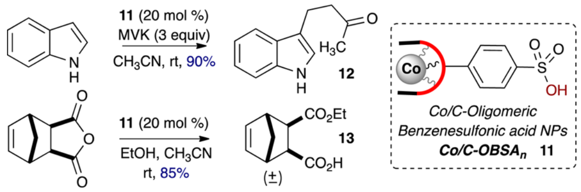


Figure 3. Regeneration of Co/C-ROMP benzenesulfonic acid NP (Co/C-OBSA$_n$) byproduct.

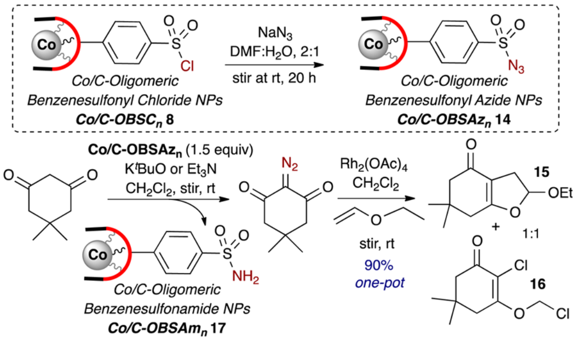
We further utilized the magnetic benzenesulfonic acid Co/C-OBSA$_n$ **11** in acid-catalyzed coupling reactions of indole with methyl vinyl ketone (MVK) as well as for the alcoholysis of exocarbic anhydride at room temperature (Scheme 3).[18] Again, the spent magnetic sulfonic acid was recovered by external magnet and the coupling products were isolated in 85–90% yield.

Scheme 3. Acid-Catalyzed Reactions Using Co/C Benzenesulfonic Acid NPs (Co/C-OBSA$_n$)



Recently sulfonyl azides have been utilized in a variety of transformations to generate various useful scaffolds.[19] Previously, our group has reported the in situ use of a soluble oligomeric benzenesulfonyl azide and facile application of diazo-transfer reactions.[14] As a result, we generated the magnetic version of benzenesulfonyl azide and utilized it in diazo-transfer reactions (Scheme 4). Magnetic decantation of the magnetic sulfonamide **17** formed in the course of the reaction allowed us to further treat the reaction mixture with $Rh_2(OAc)_4$ in the same pot, which afforded a 1:1 mixture of dihydrofuran[19c] and α-haloenones[20] in 90% overall yields.

Scheme 4. Synthesis and Utilization of Co/C Benzenesulfonyl Azide NPs (Co/C-OBSAz$_n$)



In conclusion, we have demonstrated the utilization of high-load magnetic Co/C ROMP-derived oligomeric benzenesulfonate ester Co/C-OBSE$_n$ and benzenesulfonyl chloride Co/C-

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OBSC$_n$ as efficient methylating/alkylating reagents for a variety of carboxylic acids. These alkylations were achieved by simple magnetic decantation followed by Celite filtration of the reaction mixture to remove insoluble base to derive alkylated products without the use of chromatographic purification, which makes this method suitable for automated parallel synthesis. The spent reagent, i.e., magnetic benzenesulfonic acid Co/C-OBSA$_n$ has been successfully regenerated and reused multiple times without appreciable loss of magnetic material. Current efforts are focusing on further utilization of these magnetic reagents in parallel synthesis and in one-pot protocols.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00792.

Full experimental details, copies of spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: phanson@ku.edu.

ORCID

Oliver Reiser: 0000-0003-1430-573X
Robert N. Grass: 0000-0001-6968-0823
Paul R. Hanson: 0000-0001-5356-0069

Notes

The authors declare the following competing financial interest(s): P.R.H. is on the Scientific Advisory Board of Materia, Inc.

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