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Development and Application of a Recyclable High Load Magnetic Co/C Hybrid ROMP-derived Benzene Sulfonyl Chloride Reagent and Utility of Corresponding Analogs

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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 analog sulfonic acid and *in situ* generated magnetic benzenesulfonyl azide are also reported.

Graphical abstract

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

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Full experimental details, copies of spectral data.

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area in minimizing environmental impact. Among many technologies being developed towards 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-workers³ 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 Bolm⁶ 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 SiO₂¹⁰ 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 and medicinal chemistry, but have undesirable physical characteristics that pose potential safety issues when used for routine synthesis, such as toxicity, carcinogenicity and their 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 procedure¹⁴ (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

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 of performing column chromatography (Scheme 1).¹⁵ Subsequent surface-initiated ROMP¹¹ of NB-tagged sulfonate monomer **2** using the Grubbs second-generation catalyst [G-II, C848, (IMesH₂)(PCy₃)(Cl₂)-Ru=CHPh] afforded the desired ROMPgel grafted onto the surface of the Co/C nano-beads. 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–7e** (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 gram scale by using the aforementioned ROMP protocol, which afforded hybrid ROMP-derived magnetic benzenesulfonyl chloride NPs Co/C-OBSC_n **8** (Scheme 2).

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 grey 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.

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–9h** 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).

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. Towards 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–10g**) in 72–82% yield. In all cases, the spent reagent was quantitatively retrieved by magnetic decantation of the reaction mixture.

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 SOCl₂ 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 10x) 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.

We further utilized the magnetic benzene sulfonic 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 exo-carbic 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.

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 Rh₂(OAc)₄ in the same pot, which afforded a 1:1 mixture of dihydrofuran^{19c} and α-haloenones²⁰ in 90% overall yields.

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-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 enables this method suitable for automated parallel synthesis. The spent reagent, i.e. magnetic benzenesulfonic acid Co/C-OBSA_n has been successfully regenerated and re-used 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Methylation of Various Carboxylic Acids Utilizing Magnetic Co/C-OBSE_n

Figure 2.
TEM Images of Co/C-Nb, Co/C-OBSE_n and Co/C-OBSC_n

Figure 3.
Regeneration of Co/C ROMP Benzene Sulfonic Acid NPs (Co/C-OBSE_n) Byproduct

Scheme 1. Magnetic Co/C Hybrid ROMP Benzene Sulfonate Ester NPs (Co/C-OBSE_n)

Scheme 2. Synthesis of Hybrid Magnetic Co/C ROMP Benzenesulfonyl Chloride NPs Co/C-OBSC_n

Scheme 3. Acid Catalyzed Reactions Using Co/C Benzene Sulfonic Acid NPs (Co/C-OBSA_n)

Scheme 4. Synthesis and Utilization of Co/C Benzene Sulfonyl Azide NPs (Co/C-OBSAz_n)

Table 1Methylation of Various Carboxylic Acids Utilizing Magnetic Co/C-OBSC_n

$\text{RCOOH} \xrightarrow[\text{sonication, CH}_3\text{CN, 50 } ^\circ\text{C}]{\text{MeOH, K}_2\text{CO}_3, \text{ 8 (1.5 equiv)}} \text{RCOOMe}$ <p style="text-align: center;">9a–9h</p> <div style="border: 1px dashed black; padding: 5px; display: inline-block;"> <p style="text-align: center;">Co/C-OBSC_n 8</p> </div>					
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

Table 2Alkylation of Carboxylic Acids Utilizing Magnetic (Co/C-OBSC_n)

$R^1CO_2H \xrightarrow[\text{sonication, CH}_3\text{CN, 50 } ^\circ\text{C}]{R^2OH, K_2CO_3, \text{Co/C-OBSC}_n \text{ 8}} R^1CO_2R^2$
R ² OH	product	yield(%)	R ² OH	product	yield(%)
10a) 3,5-OMe	93	EtOH	10e	82
	10b) <i>p</i> -NO ₂	95	Allyl-OH	10f	78
10c) 3,5-OMe	72	<i>n</i> BuOH	10g	80
	10d) <i>p</i> -NO ₂	75			