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Article

Sustainable Sulfonic Acid Functionalized Tubular Shape Mesoporous Silica as a Heterogeneous Catalyst for Selective Unsymmetrical Friedel–Crafts Alkylation in One Pot

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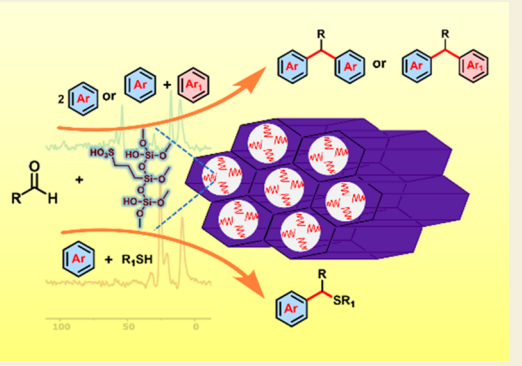
ABSTRACT: The development of general and more sustainable heterogeneous catalytic processes for Friedel–Crafts (FC) alkylation reactions is a key objective of interest for the synthesis of pharmaceuticals and commodity chemicals. Sustainable heterogeneous catalysis for the typical FC alkylation of an easily accessible carbonyl electrophile and arenes or with two different arene nucleophiles in one-pot is a prime challenge. Herein, we present a resolution to these issues through the design and utilization of a mesoporous silica catalyst that has been functionalized with sulfonic acid. For the synthesis of sulfonic acid-functionalized mesoporous silica (MSN-SO_3H), thiol-functionalized mesoporous silica was first synthesized by the co-condensation method, followed by oxidation of the thiol functionality to the sulfonic acid group. Sulfonation of mesoporous silica was confirmed by ^{13}C CP MAS NMR spectroscopy. Further, the devised heterogeneous catalysis using MSN-SO_3H has been successfully employed in the construction of diverse polyalkanes including various bioactive molecules, viz arundine, tatarinoid-C, and late-stage functionalization of natural products like menthol and Eugenol. Further, we have utilized this sustainable technique to facilitate the formation of unsymmetrical C–S bonds in a one-pot fashion. In addition, the catalyst was successfully recovered and recycled for eight cycles, demonstrating the high sustainability and cost-effectiveness of this protocol for both academic and industrial applications.



KEYWORDS: *Heterogeneous catalysis, Brønsted-acid catalysis, Friedel–Crafts, Aldehydes, Mesoporous silica, Late-stage functionalization*

Acid catalysis is among the most prominent areas of study in the field of catalysis, H_2SO_4 is the most used acid catalyst in the field of chemical manufacturing.[1] However, the use of this homogeneous acid catalyst in industry brings several challenges, which include corrosion of equipment, formation of wastewater, and always challenging handling. Because of this, considerable attention has been directed toward the immobilization of acid catalysts due to their environmental compatibility, ease of handling, and reusability. In the field of catalysis, mesoporous silica nanoparticles have garnered a lot of interest owing to the large surface area that they possess as a direct result of their pore-ordered channels.[2] In addition, mesoporous silica nanoparticles functionalized with sulfonic acids have been utilized in a wide range of catalytic reactions.[3] These reactions include the making of biodiesel,[4] acetalization reactions,[5] condensations,[6] and the preparation of biologically active compounds.[7,8,9a,10] Aboelhassan et al. synthesized a variety of sulfonic acid functionalized silica nanoparticles for the esterification of linoleic acid.[1] They found that these catalysts had exceptional performance in the esterification of linoleic acid, with a 100% conversion rate in a reaction time of about 2 h. Rhijn et al. synthesized functionalized mesoporous silica nanoparticles for catalyzing the synthesis of bisfurylalkanes and polyol esters.[7,9b] They observed that sulfonic acid functionalized mesoporous silica nanoparticles have the potential for catalyzing reactions in which zeolites fail. Hegde et al. looked at how the shape of sulfonated mesoporous silica nanoparticles affected the efficiency of making biodiesel.[2] They found that the nanocubic morphology led to a 92% conversion. Interestingly, we were highly fascinated to demonstrate this heterogeneous catalysis in the advancement of the fundamental Friedel–Crafts (FC) alkylation reaction. The FC reaction[11] is one of the oldest and most efficient tools to form a C–C bond between an electrophile and aromatic arene for synthesizing various bioactive aromatic hydrocarbons.[12a] Also, benzhydrylthioether scaffolds containing C(sp^3)–S bonds have a huge potential application in pharmaceuticals and medicinal chemistry.[12b]

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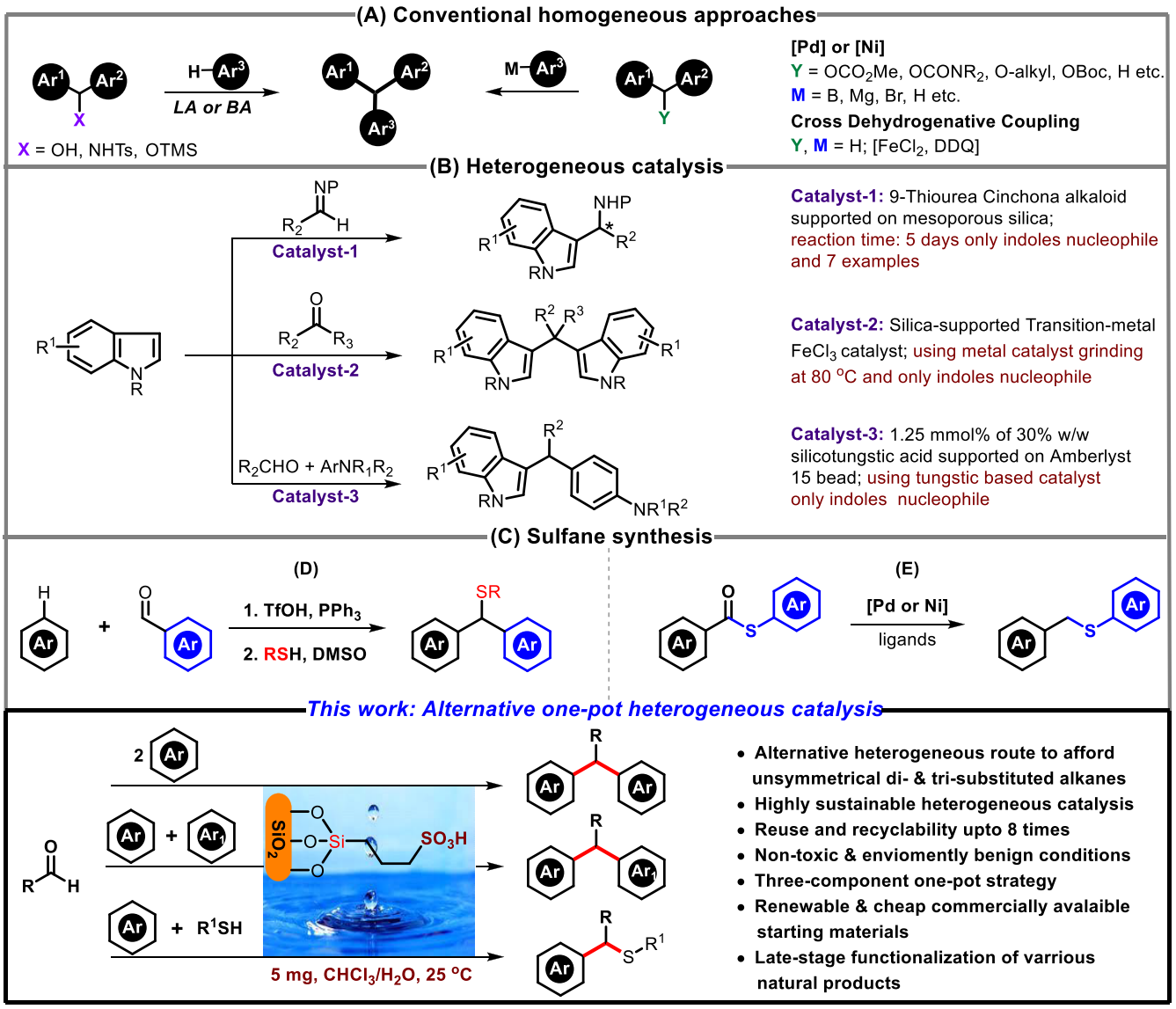
Scheme 1. Conventional Approaches and Current Developed Heterogeneous Catalysis



Generally, a homogeneous catalyst exhibits efficient activity and defined active sites, but it is always difficult to recycle. Meanwhile, a heterogeneous catalyst can easily be recycled with efficient activities. It is interesting to bridge the gap between homogeneous and heterogeneous catalysis *via* the controllable construction of a heterogeneous catalyst containing defined active sites. The industrial production of unsymmetrical polyarylated alkanes involves the usage of precious metal complexes involving various cross-coupling reactions with prefunctionalized starting materials and demands Grignard conditions (Scheme 1A),[13] and also includes homogeneous Lewis acid or Brønsted acid catalyzed FC reaction using electron-rich arenes,[14] and high stoichiometry of corrosive acids such as sulfuric acid to afford polyarylated alkanes (Scheme 1A).[1] Consequently, several methods have also been reported using solid acidic catalysts, and ionic liquids have been employed to accomplish this typical FC reaction (Scheme 1B).[15] However, many of these methods suffer from disadvantages such as unsatisfactory yields, expensive catalysts, side product formation, corrosive acids, laborious workup procedures, the requirement of a special apparatus, and harsh reaction conditions.

Giving high priority to social duties and exploration of environmentally benign synthetic methodologies, hence, this developed catalysis eliminates or reduces the use of harmful and toxic chemicals to keep it sustainable for future generations. Therefore, the development of efficient and environmentally sustainable synthetic strategies is the prime task of organic chemists in chemical science.[16] Thus, in the past decade, tremendous work has been devoted to the consideration of eco-friendly synthetic approaches in both academia and industries using solvent-free techniques,[17] water media,[18] ionic liquids,[19] solid-supported catalysts,[20] phase transfer catalysts,[21] microwave irradiation,[22] or ball-milling processes.[23] In recent years, heterogeneous catalysis or solid-supported catalysts have drawn immense interest in the development of greener synthetic strategies due to their significant merits such as high surface area, easy availability, ordered porous structure, less or no corrosion, high thermal and chemical stability, low cost and persistence in all organic solvents, no waste or disposal problems, and recyclability.

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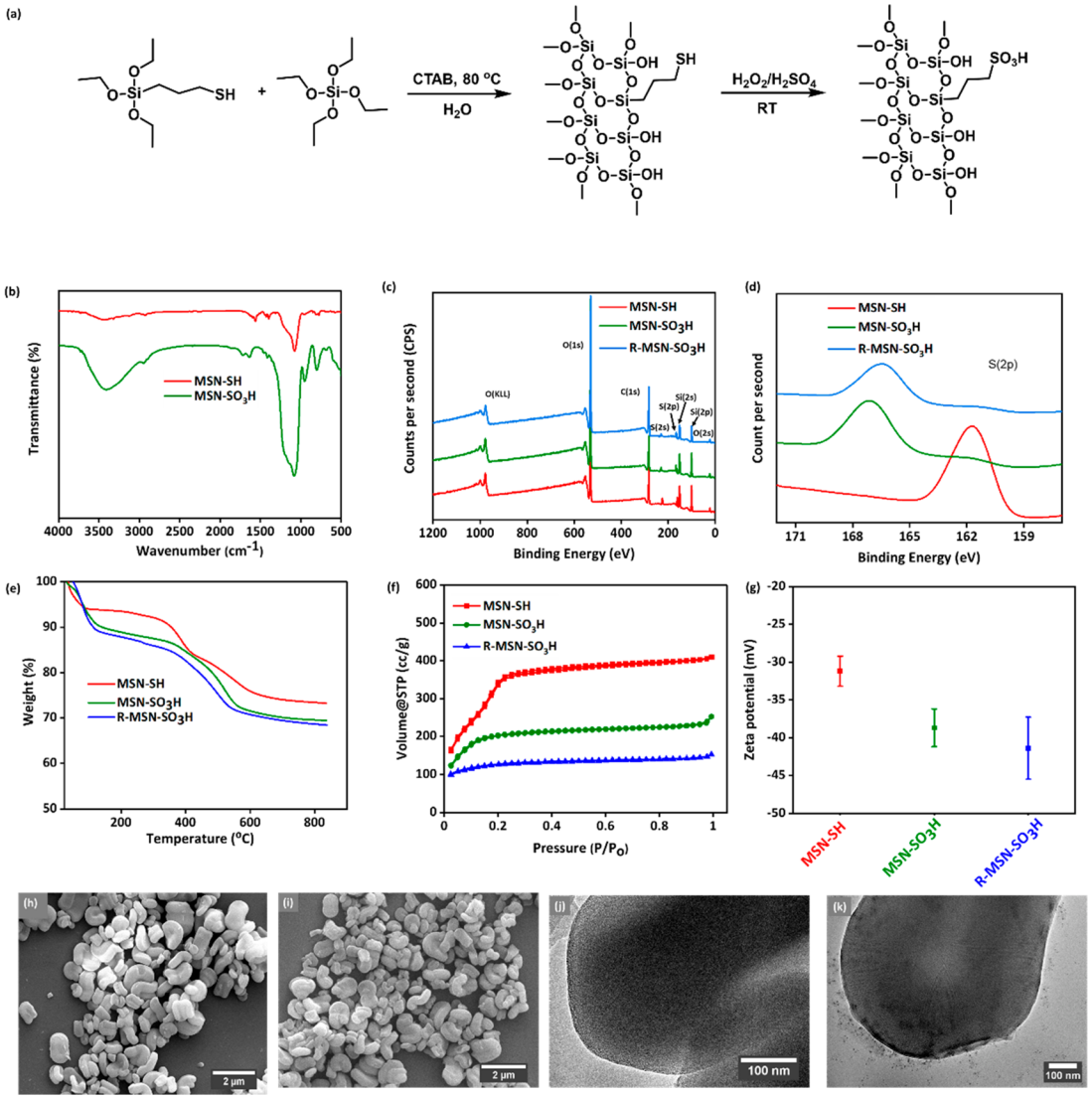

Figure 1. (a) Scheme representing synthesis of sulfonic acid functionalized mesoporous silica particles. (b) FTIR spectra of MSN-SH and MSN-SO_3H. (c) XPS spectra of MSN-SH, MSN-SO_3H, and R-MSN-SO_3H. (d) High-resolution XPS spectra for S(2p) of MSN-SH, MSN-SO_3H, and R-MSN-SO_3H. (e) TGA thermogram of MSN-SH, MSN-SO_3H and R-MSN-SO_3H. (f) BET isotherm for MSN-SH, MSN-SO_3H, and R-MSN-SO_3H. (g) Zeta potentials of MSN-SH, MSN-SO_3H, and R-MSN-SO_3H. (h) SEM micrograph of MSN-SO_3H. (i) SEM micrograph of recycled MSN-SO_3H (R-MSN-SO_3H). (j) TEM micrograph of MSN-SO_3H. (k) TEM micrograph of R-MSN-SO_3H.

Among various solid supports, silica gel is one of the extensively used solid substrate[24] for different chemical transformations in organic chemistry. Very recently, Majumdar and co-workers described silica-supported ferric chloride catalyzed an efficient heterogeneous strategy for Friedel–Crafts reaction by using indole nucleophiles only (Scheme 1B).[25a] Recently, Masarwa and the group documented a straightforward technique to access a variety of benzhydrylthioethers *via* sequential functionalization of C–H/C–P bond using organocatalyzed reaction conditions (Scheme 1D).[25b] Also, Sanford and team efficiently described a Pd and Ni-catalyzed decarbonylative C–S coupling reaction to construct thioethers by using thioesters (Scheme 1E).[25c] However, both techniques require the use of either multistep processes or metal complexes with prefunctionalized starting materials. Here, we have synthesized a sulfonated mesoporous silica nanoparticle heterogeneous catalyst to demonstrate Friedel–Crafts reaction through symmetrical/unsymmetrical C–C and C–S bond formation.

RESULTS AND DISCUSSION

Sulfonated mesoporous silica nanoparticles were synthesized by co-condensation of tetraethyl orthosilicate (TEOS) and 3-mercaptopropyltriethoxysilane (MPTES) in the presence of a structure-directing agent in a basic medium followed by oxidation of the thiol groups to $-SO_3H$ groups by using H_2O_2/H_2SO_4 resulting in mesoporous silica particles bearing an SO_3H group as shown in Figure 1a. To compare the effects of porous morphology on catalytic performance, nonporous silica nanoparticles with $-SO_3H$ groups were also synthesized. Synthesized silica particles were characterized by FTIR spectroscopy, and spectra are shown in Figure 1b. FTIR spectra of the MSN-SH silica particles exhibited characteristic vibration bands of the silica framework related to Si–O–Si asymmetric stretching at 1068 cm^{-1} and Si–O–Si symmetric stretching at 808 cm^{-1}. Additionally, a broad band centered around 3430 cm^{-1} due to the O–H stretching vibrations of hydrogen-bonded surface silanol groups was observed. The characteristic C–H stretching bands at 2990–2880 cm^{-1} are

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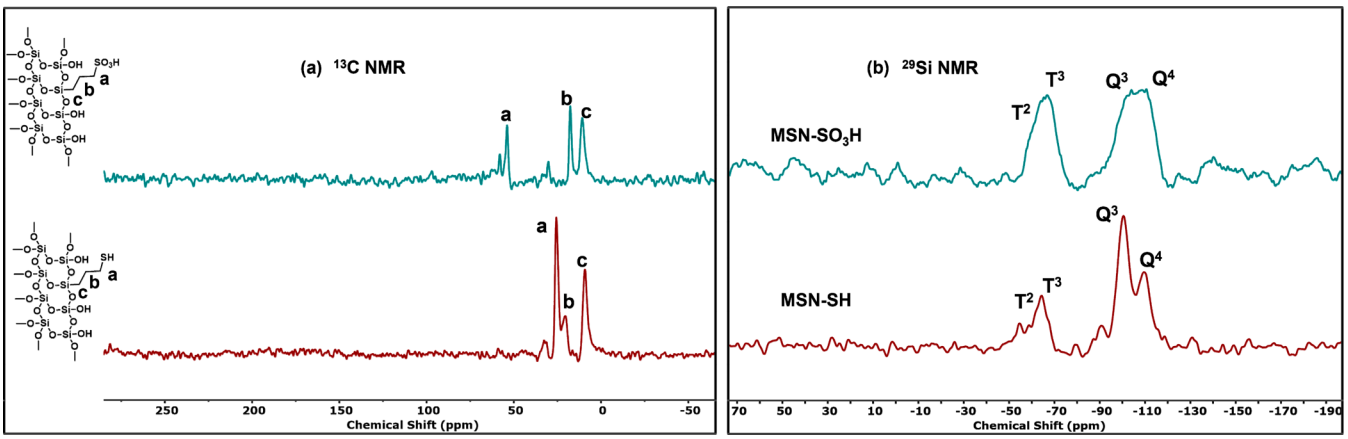

Figure 2. (a) ^{13}C CP MAS NMR spectrum of the modified mesoporous silica MSN-SH and MSN-SO_3H. (b) ^{29}Si single pulse NMR spectra of MSN-SH and MSN-SO_3H.

associated with symmetric and asymmetric vibrations of the C−H bonds of the mercaptopropyl group. Deformation vibrations of CH_2 are also observed as weak bands at 1454−1460 cm^{-1}. With the conversion of the thiol group to the sulfonic acid group, the asymmetric Si−O−Si vibration moves to 1095 cm^{-1} in the FTIR spectra of MSN-SO_3H. In addition, a weak band appears at 1420 cm^{-1} which can be attributed to the stretching vibration of the S = O bond in propyl-sulfonic acid. Further, XPS analysis was used to characterize silica samples designated as MSN-SH, MSN-SO_3H, and R-MSN-SO_3H. Figure 1c displays the overall XPS spectrum of these samples, while Figure 1d shows the high-resolution S(2p) spectra. A peak at a binding energy of 162.1 eV for the sulfur of silica particles designated as MSN-SH was observed, which increased to 167 eV for the sulfur of sulfonated silica particles designated as MSN-SO_3H and R-MSN-SO_3H. This confirms the oxidation of the -SH group to SO_3H. Furthermore, MSN-SH and MSN-SO_3H silica were characterized by ^{29}Si, and ^{13}C solid-state NMR spectroscopy, and spectra are presented in Figure 2a. These spectra gave information on the environment around the silicon as well as its organic functionalization. In ^{29}Si spectra, the signals due to the presence of a single silanol group (Q3) [$(\equiv SiO)_3SiOH$] and siloxane moiety Q4 [$(\equiv SiO)_4Si$] were found in the range −100 to −115 ppm. T2 [$(SiO)_2Si(OH)R$] and T3 [$(SiO)_3SiR$] in MSN-SH and MSN-SO_3H spectra indicate the presence of a covalently attached organic moiety (propyl thiol and propyl sulfonic acid) to silica. Signals for T2, T3, Q3, and Q4 in MSN-SH and MSN-SO_3H have been assigned in Figure 2b. ^{13}C cross-polarization magic angle spinning (CP MAS) spectra confirmed the grafting of the propyl-SH and propyl-SO_3H in MSN-SH and MSN-SO_3H as shown in Figure 2a. In order to determine the thermal stability of silica nanoparticles, TGA analysis was conducted, and a thermogram for silica particles (MSN-SH, MSN-SO_3H, and R-MSN-SO_3H) is shown in Figure 1e. As can be seen from the TGA curves, all the porous silica samples show three-step weight loss, where weight loss in the first step is due to the hydrogen bonder water, the second step involves the degradation of the sulfonic group followed by degradation of propyl group in the third step. Total weight loss due to the organic functionality of MSN-SH, MSN-SO_3H, and R-MSN-SO_3H was found to be 18.7%, 17.9%, and 19.3%, respectively. Using the nitrogen adsorption−desorption technique, the surface area, average pore size, and total pore volume of MSN-SH, MSN-SO_3H, and R-MSN-SO_3H mesoporous silica samples were determined. All silica samples exhibited Type IV adsorption isotherms, which are characteristic features of mesoporous materials, indicating that catalysis on silica particles did not alter their mesoporous structure. Figure 1f shows a shift in nitrogen uptake toward lower relative pressures, indicating a reduction in the pore volume, which was consistent with the values obtained from BET analysis.

The BET surface areas of MSN-SH, MSN-SO_3H, and R-MSN-SO_3H were determined to be 1067, 783, and 461 m^2/g, respectively. Additionally, the average pore sizes and pore volumes were measured to be 2.36, 1.996, 2.04 nm and 0.634, 0.390, 0.235 cc/g for MSN-SH, MSN-SO_3H, and R-MSN-SO_3H, respectively. The observed reduction in surface area and pore volume of MSN-SO_3H in comparison to those of MSN-SH can be attributed to the surface functionalization process, specifically the oxidation of the −SH group to the SO_3H group. Furthermore, the surface area and pore volume of the recycled samples (R-MSN-SO_3H) further decrease. This phenomenon can be ascribed to the perturbation of the pore structure resulting from multiple catalytic reactions. Additionally, this observation suggests the presence of reactants adhering to the surface of the recycled mesoporous silica. This claim is substantiated by Fourier-transform infrared spectroscopy (FTIR) (Figure S5) analysis of the recycled sample. Specifically, the presence of aromatic C−H stretching at around 3100 cm^{-1} and aromatic C═C stretching at around 1500 cm^{-1}, along with an additional bands observed at 1100−1250 cm^{-1}, further corroborates the presence of either the product or the reactants employed during the catalysis process.

Figure 1g shows the results of the zeta potential analysis used to predict the charged surface. Silica particles designated as MSN-SH show a zeta potential value of −31 mV, which decreases to −39 and −41 mV for MSN-SO_3H and R-MSN-SO_3H respectively, this can be attributed to the presence of polar groups on the particle surface of sulfonated silica (sulfonic acids). The morphology of the organically functionalized mesoporous silica was studied using FE-SEM. The FE-SEM micrographs demonstrated particle shapes and sizes. For example, MSN-SH and MSN-SO_3H showed a curved tubular morphology, as depicted in Figure 1h,i.

Interestingly, nonporous silica particles have a spherical shape, as shown in Figure S1. Several researchers have proposed various factors that govern the overall morphology

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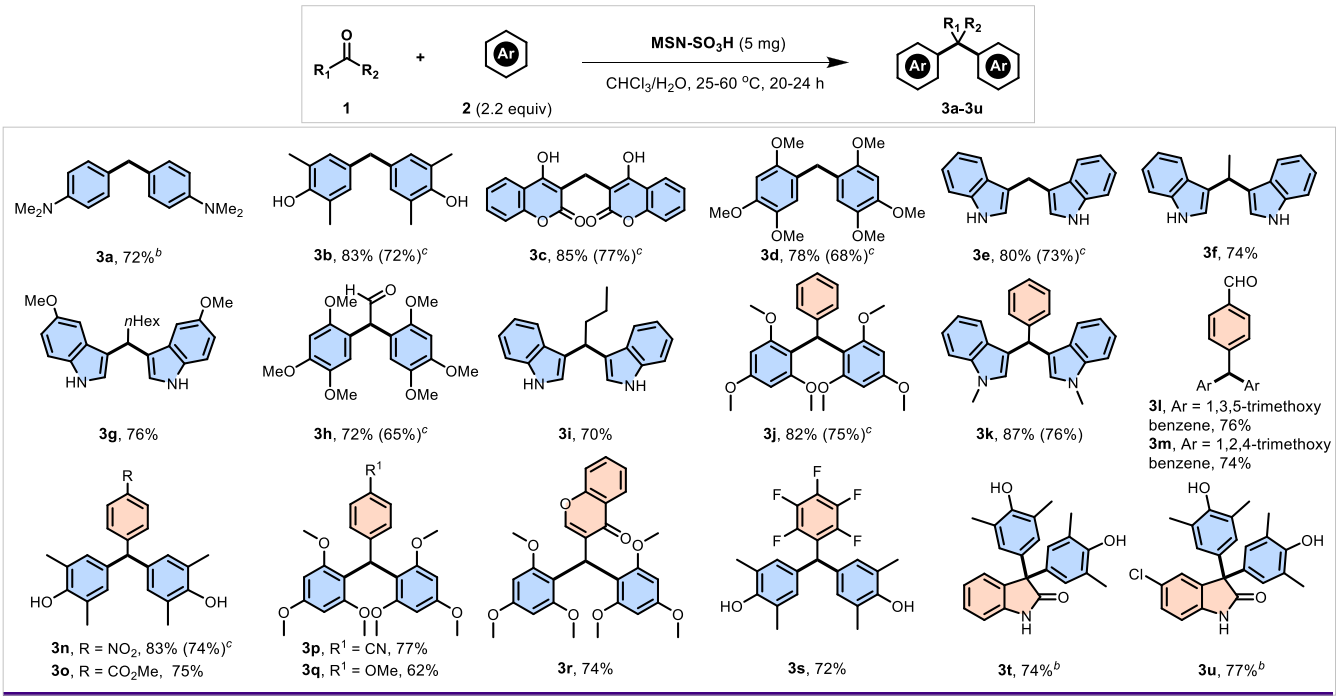
Scheme 2. Symmetrical FC Alkylation[a]



[a]Reaction conditions: **1** (1.0 equiv, 0.2 mmol), **2** (2.2 equiv, 0.44 mmol), catalyst (5.0 mg) in 0.5 mL of $CHCl_3$, 20−24 h at 25 °C. [b]Reactions were carried out at 60 °C. [c]Reactions were carried out in 0.5 mL of H_2O solvent.

of mesoporous silica particles, among them the amount and types of organoalkoxysilane, which are important factors that control the morphology of mesoporous silica particles. Such morphology can be due to the aqueous phase, where the functional group (propyl-SH) limits the intercalation of the hydrophobic groups into the surfactant micelles. A similar type of mechanism was reported by Zhang et al.[10] In addition, transmission electron microscopy (TEM) was used to further analyze the morphology of the mesoporous silica particles, and the TEM micrograph of the MSN-SO_3H sample is shown in Figure 1j. TEM analysis revealed the porous morphology of the MSN-SO_3H.

Further, small angle X-ray diffraction (XRD) patterns for MSN-SH and MSN-SO_3H silica specimens are depicted in Figure S2. Notably, the diffraction intensity of peaks originating from the d100 diffraction planes in both MSN-SH and MSN-SO_3H, occurring at 2θ values between 1.5 and 2.3, was observed. However, the reflections of other peaks corresponding to the diffraction planes (110) and (200) were not identified. The XRD peaks stemming from the (100) reflection plane manifest the hexagonal pore structures, which remain remarkably intact even following the transformation of thiol (−SH) groups into sulfonic acid (−SO_3H) moieties within the mesoporous silica framework.

Titration and FTIR of ammonia treated MSN-SO_3H have been performed to ascertain the acid content within the catalyst. In titration method, roughly 0.05 g of the sample was introduced into 15 mL of a 2 M NaCl solution and left to reach equilibrium. Subsequently, the liquid phase underwent titration through the gradual addition of 0.01 M NaOH.

The quantity of H^+ ions established through acid−base titration was 2.08 ± 0.024 mmol/g. In addition, the FTIR analysis of MSN-SO_3H before and after treatment with NH_3 was performed. The NH_3 adsorption on MSN-SO_3H exhibited characteristic N−H vibrations (occurring between 3000 and 3300 cm^{-1}) and deformations at 1410 cm^{-1} corresponding to NH_4^+ ions, along with features of bands attributable to hydroxyl groups within the range of 3600−3700 cm^{-1}. This implies the formation of NH_4^+ ions through the interaction of NH_3 with the SO_3H groups.

Sustainable heterogeneous catalysis for typical Friedel−Crafts alkylation of easily accessible carbonyl electrophiles and arenes, with two different arene nucleophiles in one-pot, is urgently required. Herein, we described a solution to these problems by using sulfuric acid functionalized solid mesoporous silica heterogeneous catalysis.

The FC reaction involving the C−C bond formation strategy is the key approach toward the synthesis of various bioactive aromatic hydrocarbons.[26] However, this process invariably requires expensive metals or a high stoichiometry of corrosive acids when using alkyl halides as electrophiles. Several issues were also encountered under these conditions, such as the formation of side products and the liberation of toxic hydrogen halides. Indeed, one of the primary focuses of this investigation is to demonstrate an atom-economical and sustainable procedure under mild reaction conditions toward achieving this goal. After the successful synthesis and characterization of sulfonic acid-functionalized mesoporous silica (MSN-SO_3H) heterogeneous catalyst. Taking these priorities in mind, we optimized the reaction conditions by varying different parameters to get the optimal reaction conditions in hand (see the Supporting Information for more details).

Substrate Scopes: Symmetrical FC Alkylation

After the screening of optimal reaction conditions in hand (0.2 mmol scale, 5 mg loading of catalyst, 0.5 mL of $CHCl_3$, 25 °C, entry 10, Table 1, Supporting Information), substrate scope

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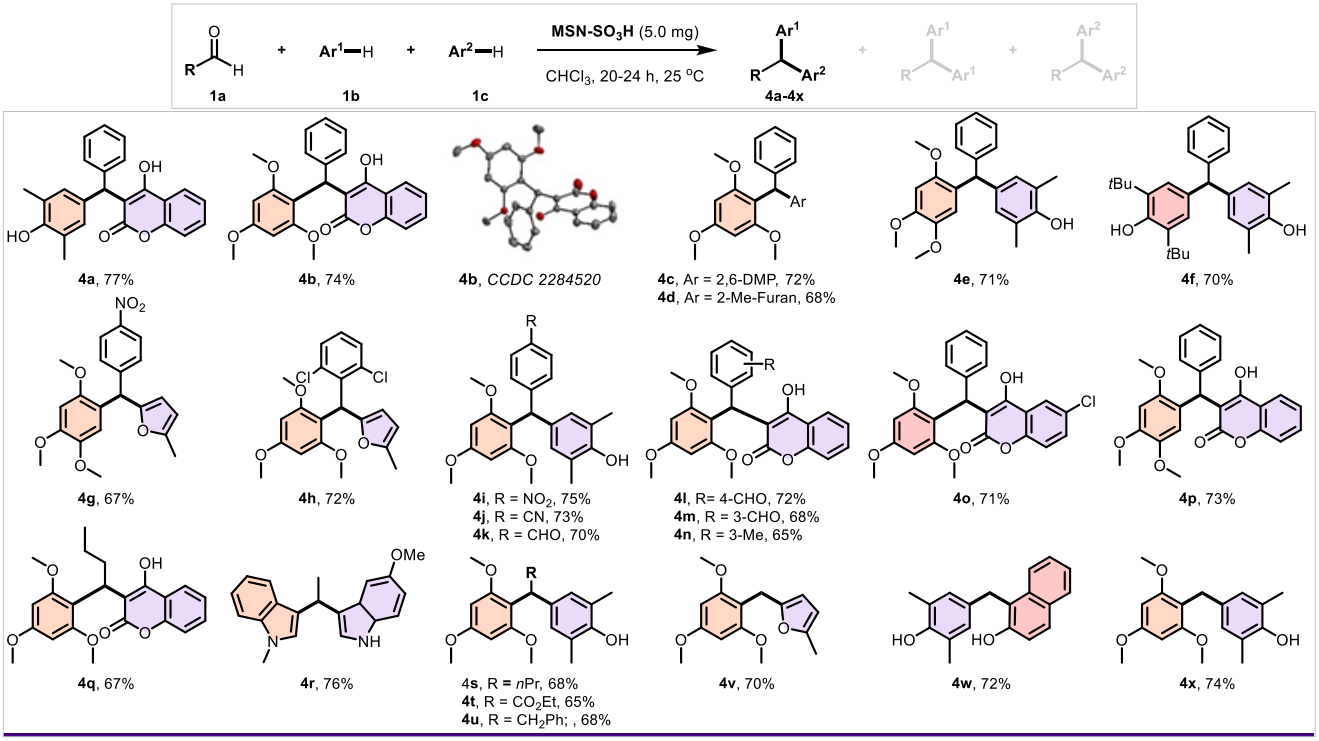
Scheme 3. Unsymmetrical FC Alkylation[a]



[a]Reaction conditions: **1a** (1.0 equiv, 0.2 mmol), **1b** (1.1 equiv, 0.22 mmol), **1c** (1.1 equiv, 0.22 mmol), catalyst (5 mg) in 0.5 mL of $CHCl_3$, 20−24 h at 25 °C.

and scalability of this developed protocol were investigated (Scheme 2). Electronically, structurally diverse and commercially available aliphatic as well as aromatic aldehydes were tested to afford symmetrical polyarylated products *via* typical FC alkylation (Scheme 2). First, we tested aliphatic aldehydes (formaldehyde, glyoxal, acetaldehyde, butyraldehyde, and heptaldehyde) under the developed standard conditions. We successfully synthesized an important class of desired diarylated products in excellent yields (**3a**−**3i**, 70−85%) with various activated arenes/(hetero) arenes nucleophiles. It is intriguing that we are curious to compare the activity of the catalyst in a more environmentally friendly solvent, water. To do this, we are subjecting a few substrates to specific conditions, using 5 mg of loading of the catalyst **1a**, 0.5 mL of H_2O, at 25 °C, as detailed in entry 13 of Table 1 in the Supporting Information. With fruitful results, we observed satisfactory isolated yields in the water solvent, showing only a slight decrease compared to the yields obtained in the $CHCl_3$ solvent. Further, using various arenes and formaldehyde under the standard reaction conditions in a water solvent, we successfully yielded the desired products in high to excellent yields (**3b**−**3e**, 68−77%). Moreover, when glyoxal and benzaldehyde derivatives were treated with various arenes and heteroarenes in a water solvent, we successfully afforded the desired polyarylated products in significant isolated yields (**3h**, **3j**, **3k**, and **3n**, 65−76%). These findings demonstrate the efficient sustainability and environmentally greener aspects of the developed heterogeneous strategy. Moreover, other arene nucleophiles, *viz*. protected aniline; phenols, 1,3,5-trimethoxy benzene (TMB), and indoles were tested successfully. Using the standard reaction conditions, 4-hydroxy-2*H*-chromen-2-one heterocyclic arene treated with formaldehyde smoothly afforded the bis-coumarin (**3c**, 85%). Further, we utilized various aromatic aldehydes in combination with a range of electronically enriched arene nucleophiles to achieve polyarylated products (**3j**−**3s**, 62−87%). Moreover, we conducted the reaction by employing benzaldehydes substituted with electron-withdrawing groups along with TMB and 2,6-dimethylphenol (2,6-DMP) as nucleophiles to afford the corresponding triarylmethanes with remarkable yields (**3l**−**3p**, 74−83%). Noteworthy, this strategy also not affect the nitrile, ester, and nitro groups, showing high functional group tolerance. Interestingly, when glyoxal and terephthalaldehyde were subjected to the optimized reaction conditions, selective condensation of one aldehyde group over another to access respective di- and triarylmethane products were obtained in high efficacy (**3h**, 72%; **3l**−**3m**, 74−76%). These desired products can further be utilized for further functionalization of the pendant CHO group *viz*. the synthesis of novel dendritic materials that can be significantly used for drug-delivery and various catalysis.[27] Benzaldehydes having electron withdrawing groups such as NO_2, CO_2Me, and CN are well tolerated giving the symmetrical products (**3n**−**3p**, 75−83%). Moreover, when benzaldehydes bearing *p*-OMe electron-donating groups were subjected to TMB treatment, the corresponding product was obtained with a satisfactory yield of 62% (**3q**) when treated with TMB. Interestingly, to check the generality of the reaction, we examine the developed protocol toward some more challenging (hetero) arene carbaldehyde and highly deactivated aldehyde to synthesize targeted molecules. In pursuit of this objective, we achieved a successful synthesis of **3r** with a yield of 74% by treating 4-oxo-4*H*-chromene-3-carbaldehyde with TMB. Desired product **3s** was synthesized with a yield of 72% by treating pentafluorobenzaldehyde with a

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2,6-DMP arene nucleophile. Interestingly, we were intrigued by the significant applicability of the established protocol to various types of carbonyl electrophiles. Notably, we observed that the heterogeneous FC arylation on isatin derivatives was also successfully implemented to synthesize tetra-substituted derivatives. Employing activated arenes results in the formation of desired products that are obtained with high efficiency (**3t**−**3u**, 74−77%).

Substrate Scope: Unsymmetrical FC Alkylation

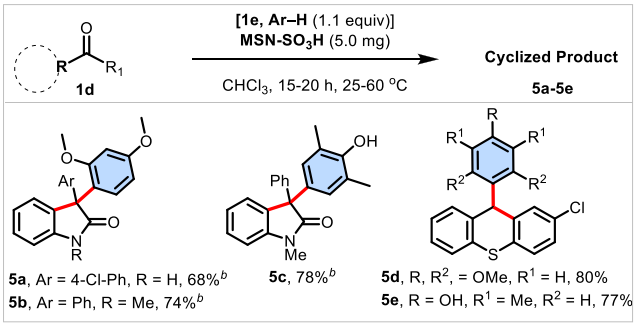
Furthermore, in order to assess the universality of the current procedure across a wide range of two distinct arene nucleophiles, we aimed to generate a diverse library of valuable unsymmetrical products by using a convenient one-pot strategy (Scheme 3). Due to the finite feasibility of the formation of homocoupled symmetrical products when two different arene nucleophiles are treated with electrophile in a one-pot strategy is always challenging.[28] Using our developed heterogeneous FC alkylation approach, we have achieved the synthesis of a unique library of electronically and structurally diverse di- and trisubstituted unsymmetrical polyarylated alkanes. The procedure has demonstrated good to excellent yields, with only trace amounts of homocoupled symmetrical products. Under optimum reaction conditions, we observed the predominant formation of desired unsymmetrical products (**4a**−**4f**) in significant yields (68−77%) when benzaldehyde was treated with the combination of two distinct types of arenes and heteroarene nucleophiles. The reaction of benzaldehyde-bearing electron-withdrawing functional groups *viz*. NO_2, CHO, CN, and halogens proceeded in high efficiency with the coupling of two different arene nucleophiles (**4g**−**4m**, 67−75%). Gratifyingly, potentially reactive functional groups were well tolerated under the developed reaction conditions. Also, successful functionalization of *ortho*-dichloro substituted benzaldehyde treated with TMB and 2-methyl furan nucleophiles led to the formation of the desired unsymmetrical product (**4h**) in a high yield of 72%. Interestingly, like the above observations, starting material that possesses poly aldehydic functionality, we condensed selectively one −CHO group that gives valuable unsymmetrical alkylated products in excellent yields. Consequently, by subjecting terephthalaldehyde to the combination of 2,6-DMP and TMB nucleophiles, a selective −CHO condensed desired unsymmetrical product was achieved in excellent yield (**4k**, 70%). Similarly, terephthalaldeyde and isophthalaldehyde were successfully utilized to condense selectively one −CHO group by subjecting TMB and 4-hydroxycoumarin nucleophile partners with high efficacy (**4l**−**4m**, 68−72%). While Nair and co-workers demonstrated the condensation reaction of both −CHO groups in dialdehydes when treated with electron-rich arenes under the influence of gold(III).[27] We next turned our focus to exploring the diversity of the present heterogeneous reaction toward various aliphatic aldehydes. Unsymmetrical diarylmethanes are a highly demanding class of molecules from a pharma and medicinal chemistry point of view.[26] To afford this important class of molecules, previous strategies always demand prefunctionalized starting materials, the expansive and high stoichiometry of catalyst loading under harsh reaction conditions.[29] In addition, the reaction of butyraldehyde with TMB and 4-hydroxy coumarin efficiently afforded the corresponding unsymmetrical product (**4q**, 67%). The current methodology also successfully facilitated a seamless FC reaction between acetaldehyde and two distinct indole derivatives, resulting in the synthesis of desired unsymmetrical bis-indolyl product (**4r**, 76%). Remarkably, when employed by the combined influence of TMB and 2,6-DMP arene nucleophiles, ethyl-2-oxoacetate and 2-phenylacetaldehyde underwent the formation of unsymmetrical diaryl compounds (**4s**−**4u**) in yields ranging from 65% to 68%.

Furthermore, we synthesized various unsymmetrical diarylated compounds (**4v**−**4x**, 70%−74%) by using readily available paraformaldehyde and distinct coupling partners such as arenes/heteroarenes. This accomplishment is particularly noteworthy, as it is a consistently challenging task (Scheme 3).

Next, we also examined this technique to achieve inter- and intramolecular FC cyclization simultaneously in a one-pot manner (Scheme 4). By utilizing α-ketoamide and methyl-protected α-ketoamide electrophiles, along with a 1,3-dimethoxybenzene nucleophile, we successfully synthesized 3,3-disubstituted 2-oxindole derivatives through cyclization in high yields (**5a**, **5b**, 68−74%). Also, 2,6-DMP arene was successfully treated with methyl-protected α-ketoamide to synthesize the desired cyclized oxindole derivative (**5c**, 78%). Interestingly, we synthesized cyclic thioxanthene derivatives **5d**, **5e** in similarly high yields (77−80%) by subjecting 2-((4-chlorophenyl)thio)benzaldehyde to treatment with TMB and 2,6-DMP arenes.

In addition, we were curious to apply this developed heterogeneous catalytic strategy to construct unsymmetrical C−S bonds using a one-pot strategy. To further broaden the scope, we synthesized an interesting class of sulfanes derivatives by treating various aldehydes with thiols and arene nucleophiles in one-pot fashion under optimized reaction conditions (Scheme 5). As expected, we successfully applied this procedure to formaldehyde by treating it with naphthalene-2-thiol and TMB to afford the desired product **6a** in 76% yield through unsymmetrical C−S bond formation. Furthermore, aliphatic thiol phenylmethanethiol in combination with 2,6-DMP or TMB arene nucleophiles synthesized the corresponding unsymmetrical sulfanes in good to excellent yields (**6b**, **6c**, 68−71%). Also, benzaldehyde and *p*-NO_2-benzaldeyde efficiently exploited into desired unsymmetrical sulfane (**6d**−**6h**, 71−78%) when various arenes and thiols were taken as nucleophilic partners.

Scheme 4[a]



[a]Reaction conditions: **1d** (1.0 equiv, 0.2 mmol), **1e** (1.1 equiv, 0.22 mmol), catalyst (5 mg) in 0.5 mL of $CHCl_3$, 15−20 h at 25 °C. [b]Reactions were carried out at 60 °C.

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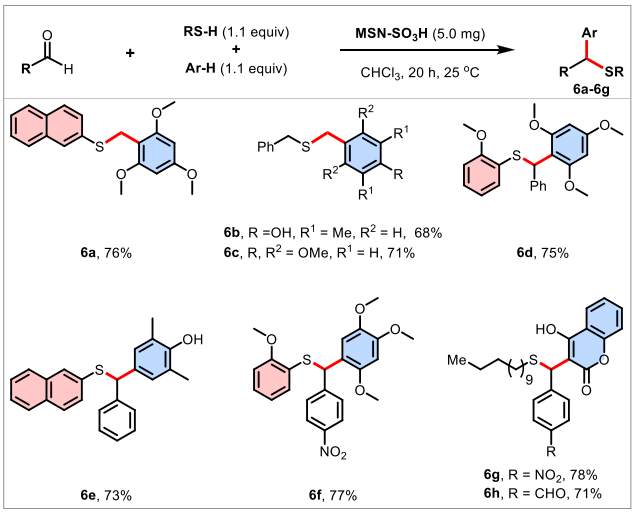
Scheme 5[a]

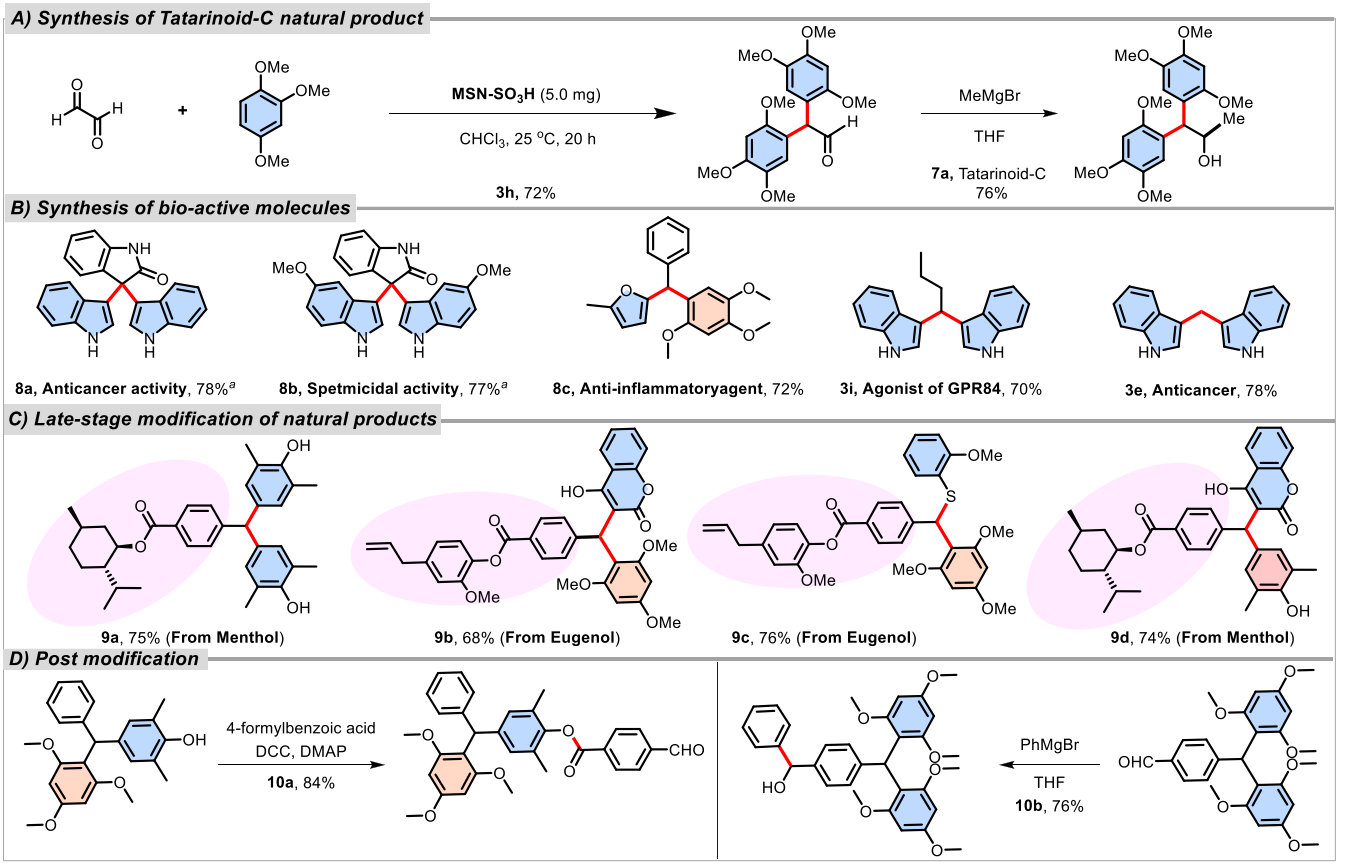


[a]Reaction conditions: aldehydes (1.0 equiv, 0.2 mmol), arenes (1.1 equiv, 0.22 mmol), thiols (1.1 equiv, 0.22 mmol), and catalyst (5 mg) in 0.5 mL of $CHCl_3$, 20 h at 25 °C.

Applications

To demonstrate the synthetic application of the developed protocol, we applied this heterogeneous strategy to the production of various bioactive molecules and natural products (Scheme 6). Remarkably, we have successfully documented the first heterogeneous synthetic route to synthesize (±)-Tatarinoid-C natural product. To achieve this goal, we applied FC arylation on glyoxal by using the 1,2,4-TMB nucleophile, followed by the Grignard reaction in the facile synthesis of (±)-Tatarinoid-C natural product (**7a**, 76%). Conventional synthetic route demands multiple steps and prefunctionalization to synthesize (±)-Tatarinoid-C natural product with several side products formation causing overall low conversion.[30] Noteworthy, toward the demonstration of the process, we have also synthesized several important heterocyclic 3,3-di(indolyl) indolin-2-ones pharmaceutically active drug molecules. By using the optimized reaction conditions, isatin reacted with indole to afford a bioactive molecule (**8a**, 78%) having potent anticancer activities. Spetmicidal bioactive agent (**8b**, 77%) was efficiently synthesized when isatin was treated with 5-methoxy indole. Also, we successfully synthesized an unsymmetrical anti-inflammatory bioactive molecule (**8c**, 72%) by treating benzaldehyde with 1,2,4-TMB and 2-Me-furan. Synthesis of bis(indolyl) alkane, an agonist of GPR84 was efficiently achieved by subjecting butyraldehyde with indole nucleophile in high yield (**8d**, 80%). Fascinatingly, to display the potential applicability of the current protocol, we applied it to the late-stage functionalization and modification of various natural products (Scheme 6). To our delight, this FC heterogeneous catalytical strategy is

Scheme 6. Application and Utility of the Developed Protocol[b]



[b](A) Facile synthesis of Tatarinoid-C natural product. (B) Synthesis of some important bioactive molecules. [a]Reactions were carried out at 60 °C. (C) Functionalization of various natural products through late-stage modification. (D) Further postmodification of TRAMs product.

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highly efficient in the late-stage modification of natural products like Eugenol and Menthol. The natural product Menthol was subjected to functionalization with 2,6-DMP arene nucleophile, resulting in the synthesis of desired symmetrical polyarylated product (**9a**, 75%). Also, Eugenol and Menthol were successfully utilized in unsymmetrical FC arylation to construct the C−C bond by subjecting distinct arene nucleophiles (**9b**, **9d**, 68−74%). Notably, this methodology has facilitated the formation of an unsymmetrical C−S bond, demonstrating the versatility and utility of the protocol to generate diverse chemical structures. With great success, we employed the natural product Eugenol with TMB and 2-OMe-thiophenol in unsymmetrical C−S bond formation and synthesized the desired product **9c** in 76% isolated yield. In order to show the organic synthetic transformation, a synthesized symmetrical TRAM molecule (**3l**) was efficiently modified into formylbenzoate using a DCC coupling reaction condition (**10a**, 84%).

In addition, an unsymmetrical TRAM molecule (**4c**) was functionalized by employing the Grignard reaction to afford the corresponding carbinol in an excellent yield (**10b**, 76%). These synthesized molecules can be further utilized in the synthesis of various important complex dendrimers (see the Supporting Information for more details). Furthermore, the Mesoporous catalyst could be recycled and reused at least eight times with a slight decrease in the conversion (Figure 3).

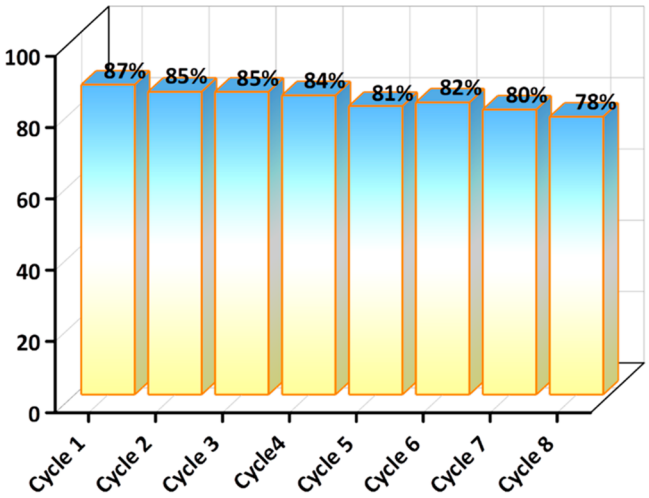
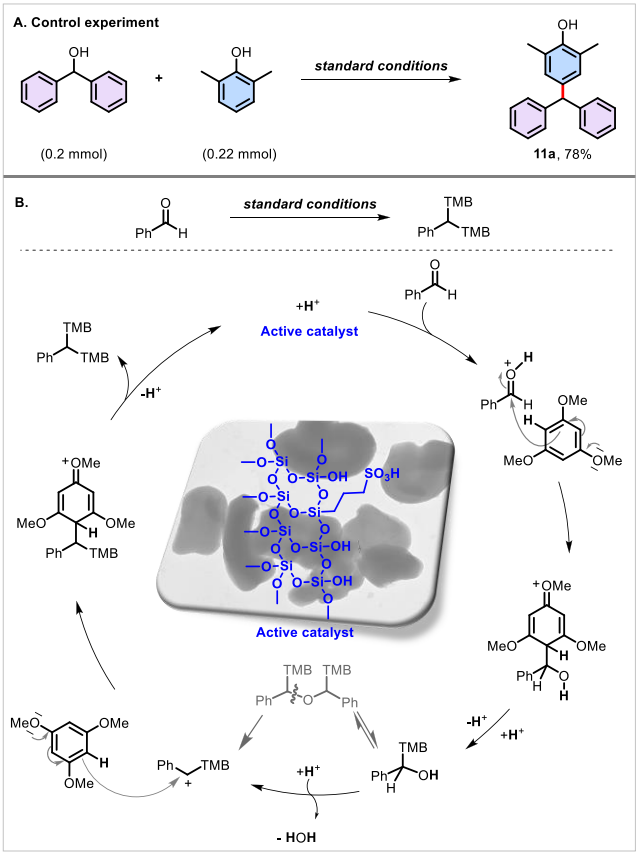


Figure 3. Recycling and reusability of the MSN-SO_3H catalyst up to eight cycles.

We have conducted an investigation on the catalytic recyclability of the MSN-SO_3H catalyst in the reaction between TMB and benzaldehyde. Upon completion of the reaction, the catalyst was filtered and the products were dissolved in either ethyl acetate or dichloromethane. After several washes and drying under vacuum, the catalyst was then used in the subsequent cycle. The results (87% initial, 85%, 85%, 84%, 81%, 82%, 80%, and 78%) clearly showed a negligible decline in the catalytic efficiency in each successive cycle.

The SEM and TEM micrographs of the recycled MSN-SO_3H are shown in Figure 1i, k. The result indicated that the shape, size, and mesopores of MSN-SO_3H were not affected even after eight times of repeated use of the catalyst. To understand the mechanism of Brønsted acid-catalyzed double arylation reaction, we have performed control experiments to know whether the reaction is going through alcohol as an intermediate. Under the standard reaction conditions, using diphenylmethanol gives the corresponding arylated product (**11a**, 78%, Scheme 7).

Scheme 7[a]



[a](A) Control experiment and (B) proposed catalytic cycle.

Moreover, based on previous studies, possible reaction mechanisms involving in situ generated Brønsted acid potentially played the role of the active catalyst.[14]

In summary, we have successfully synthesized the sulfonic acid-functionalized mesoporous silica (MSN-SO_3H). The functionalization of mesoporous silica was confirmed by FTIR, XPS, TGA, ^{13}C CP MAS NMR, and ^{29}Si solid-state NMR. The organic functionalization of MSN-SO_3 was observed to be 17.9%. The tubular shape of the synthesized silica was confirmed by SEM. The porous structure of the synthesized silica was confirmed by BET and TEM. Further, synthesized MSN-SO_3H was utilized as a highly sustainable heterogeneous catalyst for the Friedel−Crafts reaction. The developed catalyst was successfully demonstrated to synthesize a huge library of C−C, C−S, and various cyclized molecules. The potent utility of this strategy was demonstrated by synthesizing many important bioactive symmetrical and unsymmetrical diaryl and triarylmethanes and gram-scale reactions. Also, the current approach has also been applied for the late-stage functionalization of important natural products, such as menthol, Eugenol, etc. The used sulfonic acid-functionalized mesoporous silica catalyst was successfully recycled and reused for up to eight cycles, making this reaction

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highly sustainable and economical. Further demonstration of this strategy for developing other reactions with more challenging electrophiles such as ketones and esters and their enantioselective versions are currently underway in our laboratory.

METHODS

Synthesis of Thiol-Functionalized Mesoporous Silica Nanoparticles (Figure 1a)

For the synthesis of thiol-functionalized mesoporous silica, a mixture of CTAB (cetyltrimethylammonium bromide) (5.48 mmol, 2.0 g), 2 M NaOH (6.8 mL), and H_2O (480 g) was heated at 80 °C for 20 min. To this clear solution, TEOS (Tetraethyl orthosilicate) (40.4 mmol) and 3-mercaptopropyltriethoxy silane (10.1 mmol) were added rapidly by using a syringe. Following the addition, white precipitate was observed after 3 min of stirring at 600 rpm. The reaction temperature was maintained at 80 °C for 2 h. The product was isolated and washed with water by using centrifugation for 5 min. To remove the CTAB template, acid extractions were performed in a mixture of ethanol (250 mL), and 7.0 g hydrochloric acid (36%) at 80 °C for 8 h and the procedure was repeated six times. Resulting template-removed silica particles were washed with water and ethanol, and then dried under vacuum. Yield 2.0 g. Synthesized functionalized mesoporous silica particles were further characterized using FESEM, TEM, FTIR, and TGA.

Synthesis of Sulfonated Mesoporous Silica Nanoparticles (Figure 1a)

Synthesis of MSN-SO_3H was done by oxidation of MSN-SH. MSN-SH (2.0 g) was mixed with 30% (v/v) H_2O_2 (80 mL; 2.66 mol) at room temperature for 24 h. After 12 h, a few drops of strong sulfuric acid were added, and the reaction was stirred for another 12 h. The solid was rinsed many times with water by centrifugation before being dried overnight at 100 °C.

General Procedure for the Synthesis of Symmetrical Triarylmethanes/Diarylmethanes (Scheme 2)

To a 5 mL round-bottom flask equipped with a magnetic stir bar was sequentially added the aldehyde (0.2 mmol, 1.0 equiv), MSN-SO_3H (5.0 mg), and the arene nucleophiles (0.44 mmol, 2.2 equiv) in 0.5 mL of $CHCl_3$ solvent at 25 °C. Further, the reaction mixture was stirred at 25−60 °C for 20−24 h. After completion, the reaction was monitored via a TLC plate in 10−20% EtOAc in hexane. The solvent was removed under reduced pressure to get the crude product. Further, column chromatography was carried out over silica gel (100−200) mesh using a mixture of hexane and ethyl acetate to purify the crude product.

General Procedure for Unsymmetrical Friedel−Crafts Arylation (Scheme 3)

To a 5 mL round-bottom flask equipped with a magnetic stir bar was sequentially added the two different aryl nucleophiles (0.22 mmol, 1.1 equiv each), aldehyde (0.2 mmol, 1.0 equiv), and MSN-SO_3H (5.0 mg), in 0.5 mL $CHCl_3$ solvent at room temperature (25 °C). Further, the reaction mixture was stirred at room temperature for 20−24 h. The completion of the reaction was monitored via a TLC plate in 20% EtOAc in hexane. The solvent was removed under reduced pressure to get the crude product. Further, column chromatography was carried out over silica gel (100−200) mesh using a mixture of hexane and ethyl acetate to purify the crude product.

General Procedure for the Friedel−Crafts Cyclization Reactions (Scheme 4)

To a 5 mL round-bottom flask equipped with a magnetic stir bar was sequentially added the substrate (aldehydes or acetamide) (0.2 mmol, 1.0 equiv), MSN-SO_3H (5.0 mg), and the arene nucleophiles (0.22 mmol, 1.1 equiv), in 0.5 mL $CHCl_3$ solvent at 25 °C. Further, the reaction mixture was stirred at 25−60 °C for 20−24 h. After completion, the reaction was monitored via a TLC plate in 10−20% EtOAc in hexane. The solvent was removed under reduced pressure to obtain the crude product. Further, column chromatography was carried out over silica gel (100−200) mesh using a mixture of hexane and ethyl acetate to purify the crude product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00563.

Crystallographic data (TXT)

Detailed experimental procedures and characterization of new compounds (PDF)

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Author Contributions

C.K.H. and L.N. supervised this study. The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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