Article

Application of Silver Nanoparticles in the Multicomponent Reaction Domain: A Combined Catalytic Reduction Methodology to Efficiently Access Potential Hypertension or Inflammation Inhibitors

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ABSTRACT: The catalytic efficacy of silver nanoparticles was investigated toward the chemoselective reduction of nitro-tetrazole or amino acid-substituted derivatives into the corresponding amines in high isolated yields. This highly efficient protocol was thereafter applied toward the multicomponent reaction synthesis of heterocyclic dihydroquinolin-2-ones with high isolated yields. The reaction proceeds with low catalyst loading (0.8–1.4 mol %) and under mild catalytic conditions, a very good functional-group tolerance, and high yields and can be easily scaled up to more than 1 mmol of product. Thus, the present catalytic methodology highlights a useful synthetic application. Different molecules are designed and accordingly synthesized with the current protocol that could play the role of inhibitors of the soluble epoxide hydrolase, an important target for therapies against hypertension or inflammation.

INTRODUCTION

The discovery of combinatorial methodologies to yield organic scaffolds in more efficient ways, such as waste reduction, cost, and less energy demanding, is a key challenge in synthetic chemistry. More specifically, the reduction of the nitro group may yield amines and this fundamental transformation is frequently used in the synthesis of pharmaceuticals, agrochemicals, dye intermediates, and pigments, as well as for a variety of fine chemicals.1 The most promising route for the conversion of $\text{NO}_2^-$ to $\text{NH}_2$ is the transition metal-catalyzed hydrogenation process,2 but the observed chemoselectivity is rather low, especially when other reducible groups are present. In this direction, noble metal nanoparticles such as gold (AuNPs)3–6 and silver (AgNPs),5,6 as well as cobalt, iron, and manganese-based compounds or oxides7–9 have been employed as catalysts in the reduction of nitro aromatic compounds. Both hydrogenation and transfer hydrogenation processes have been successfully used for the selective nitro group reduction to the corresponding amine but have significant drawbacks. The former requires high temperatures and $\text{H}_2$ pressures and is applicable in monosubstituted aromatic nitro compounds; however, transfer hydrogenation is a chemoselective process employed at ambient conditions using several reducing agents such as borohydrides, hydrosilanes, CO/H$_2$O, and HCOONH$_4$.‡ Therefore, the development of new protocols and synthetic strategies that will provide complex as well as functionalized molecules, not only efficient but also chemoselectively, environmentally benign as well as tolerant, including a diverse array of functional moieties and protecting groups, is of high interest and value.10,11

Multicomponent reactions (MCRs) are very often tagged as atom-economic, step-efficient with high exploratory power with regard to chemical space, processes.12,13 Using the MCR principle, rapid and easy access to organic scaffolds with high diversity (more than 500 different scaffolds) can be achieved. Consequently, the industrial and academic synthetic community uses this method to design and discover biologically active compounds applicable in medicinal chemistry and drug discovery.14 In addition, MCRs are the perfect example of a synthetic hub;13 they are highly compatible with a range of unprotected orthogonal functional groups, thus permitting subsequent transformations on a second level.12,15–17 The degree of diversity and complexity that can be achieved following this protocol is highly increased, and therefore the discovery of new methodologies that will postmodify the original MCR “core” is of great importance and value.

So far, we have demonstrated the catalytic efficacy of supported AuNPs and AgNPs on mesoporous titania and silica...
(Au/TiO₂, Ag/TiO₂, and Ag/HMS), toward the chemoselective reduction (via transfer hydrogenation) of a series of aromatic nitroarenes to the corresponding anilines and/or N-aryl hydroxylamines under mild conditions and applying fast and clean reaction processes.¹⁸⁻²² In all cases, simple borohydrides, boranes, hydrosilanes, and hydrazine were used as reducing agents (Scheme 1). Building on these findings, we attempt herein to combine—for the first time—the application of these catalytic systems in the highly diverse and complex environment of the MCR chemical space. More specifically, the Ag/HMS−NaBH₄ system was employed to reduce selectively the nitro groups in the presence of other easily reducible moieties such as carbonyl, amide, ester, and halogen, without the need of a protecting group (Scheme 1). In addition, the one-pot synthesis of several N-substituted dihydroquinoxalin-2-ones was studied under the present catalytic conditions, providing an exceptional and mild synthetic approach based on the reported chemoselective transfer hydrogenation process of the multifunctional nitro precursors (Scheme 1).

The present catalytic protocol is timely and of high interest as it has a selective and sustainable synthetic character permitting further diversification of the synthesized MCR libraries and giving access to multifunctional amines and dihydroquinoxalinones.

# RESULTS AND DISCUSSION

In this work, three variants of one of the most well-known isocyanide-based MCRs¹²⁻¹⁵,²³ were employed; such as the Ugi-Smiles,²⁴⁻²⁶ the Ugi-tetrazole (UT-4CR),²⁷⁻³³ and the classical Ugi reaction (U-4CR).²²⁻²⁶,³⁵ We highly diversified the aforementioned reactions including a variety of functional groups (their synthetic schemes are presented in detail in Supporting Information). For the catalytic reductions, we employed commercially available supported AuNPs Au/TiO₂, as well as the salts AgNO₃ and AgOTf and the synthesized mesoporous catalysts Ag/TiO₂ and Ag/HMS.²¹,²² The commercial catalyst Au/TiO₂ features a ca. 1 wt % Au loading and exhibits an average AuNP size of about 2⁻3 nm. Mesoporous Ag/TiO₂ composite with an AgNP loading amount of 4 wt % and an average size of about 4⁻7 nm was prepared by photochemical deposition of AgNPs on the surface of NP-based mesoporous titania.²¹ Also, Ag/HMS with AgNP loading amounts of 10, 30, and 50 wt % and the size of particles ranged between 15 and 30 nm (Table S1) were synthesized by the in situ deposition/reduction with a mixture of ethanolamine and ethylenediamine, described in details in our previous work on the selective reduction of azines to benzyl hydrazones.²² For selected transmission electron microscopy (TEM) and scanning electron microscopy (SEM) images, see also Supporting Information (Figure S1).

The reduction of nitro multifunctional derivative 1 toward the corresponding amine 1a was initially investigated in order to optimize the reaction conditions, using supported AgNPs as the catalyst, different hydrides, solvents, and catalysts (Table 1). Under the present conditions described below, the common reducing agents NaBH₄, LiAlH₄, and NaH were found to be inactive in the absence of catalyst (Table 1, entries 1⁻4); furthermore, degradation products (cleavage of the tert-amide of the anisole group) were observed by the ¹H NMR of the crude mixtures in the two latter cases. In addition, the presence of only 1,1,3,3-tetramethyl disiloxane (TMDS) does not lead to any reduction process (Table 1, entry 5).

To our delight, NaBH₄ and TMDS in the presence of Au/TiO₂ provided an efficient reduction, Table 1, entries
Table 1. Evaluation of Catalysts, Reducing Agents, and Solvents in the Catalytic Reduction of 1 into 1a

| entry | catalyst | solvent | reducing agent | time (h) | 1%/1a% |
|-------|----------|---------|----------------|---------|--------|
| 1     | Au/TiO2  | MeOH    | NaBH4          | 18      | 100/0  |
| 2     | Au/TiO2  | THF/MEOH| NaBH4          | 18      | 100/0  |
| 3     | THF      | LiAlH4  | 18             | 43/0    |
| 4     | THF      | NaH     | 18             | 47/0    |
| 5     | THF/MeOH | TMS     | 24             | 100/0   |
| 6     | Au/TiO2  | THF/MeOH| NaBH4          | 1       | 0/99   |
| 7     | Au/TiO2  | THF/MeOH| TMS            | 1       | 0/99   |
| 8     | Au/TiO2  | MeOH    | TMS            | 1       | 0/99   |
| 9     | Ag/TiO2  | THF/MeOH| NaBH4          | 18      | 3/97   |
| 10    | Ag/TiO2  | MeOH    | NaBH4          | 18      | 5/95   |
| 11    | Ag/HMS(10)| MeOH    | NaBH4          | 18      | 0/99   |
| 12    | Ag/HMS(10)| THF/MeOH| NaBH4          | 1       | 0/99   |
| 13    | Ag/HMS(10)| THF/MeOH| NaBH4          | 1       | 60/40  |
| 14    | Ag/HMS(10)| THF/MeOH| TMS            | 1       | 100/0  |
| 15    | Ag/HMS(10)| THF/MeOH| Et3SiH         | 18      | 100/0  |
| 16    | Ag/HMS(30)| THF/MeOH| NaBH4          | 1       | 0/99   |
| 17    | Ag/HMS(50)| THF/MeOH| NaBH4          | 1       | 5/95   |
| 18    | HMS      | THF/MeOH| NaBH4          | 1       | 100/0  |
| 19    | AgOTf    | THF/MeOH| NaBH4          | 1       | 2/98   |
| 20    | AgOTf    | THF/MeOH| NaBH4          | 1       | 7/93   |

*Conditions: 20 mg of the Au/TiO2 or 10 mg of the Ag/TiO2 (ca. 0.8 mol %) or 3 mg of the Ag/HMS (ca. 1, 4, and 7 mol %), 0.2 mmol of 1, 0.8 mmol of the hydrosilanes or 0.4 mmol of the sodium borohydride, 1 mL of solvent mixture, at rt. Relative yields of 1 and 1a at appropriate time measured by 1H NMR of the crude reduction mixture. Unidentified products missing either the tert-amide or the anisole group from its structure as determined by 1H NMR in some cases. Equimolar amount of the reducing agent was used. All the salts were used in 20 mmol %.

In addition, Ag NPs (Ag/TiO2) were found to catalyze the quantitative formation of the corresponding amine 1a using NaBH4 as the reducing agent (Table 1, entries 9 and 10). However, for better solubility of the starting material, we continue our further screening tests with the equimolar mixture of THF/MeOH. To compare the catalytic activity of the present synthesized Ag/HMS catalysts, we studied the reduction of 1, with Ag/HMS (x), (x = 10, 30, and 50%), catalysts in the presence of NaBH4 and the equimolar mixture of methanol/THF as solvent. All catalysts found to lead the transfer hydrogenation process to completion in a fast and clean manner, in high isolated yield >95%, without the requirement of any chromatographic purification of the product 1a (Table 1, entries 11−17). The Ag/HMS (10) and the Ag/HMS (30) catalysts, with an average of AgNP size below 20 nm, showed the best catalytic activity in terms of the conversion and selectivity of 1a in the presence of two equivalents of NaBH4 (Table 1, entries 12 and 16). This result supports a high relationship between the silver loading amount and the Ag particle size with the reaction selectivity toward 1. In comparison, yields dramatically decreased when an equimolar amount of NaBH4 was used (Table 1, entry 13); however in the absence of AgNPs (HMS) no conversion of 1 to 1a was observed (Table 1, entry 18). On the other hand, in the presence of hydrosilanes TMDS and Et3SiH, no reactions occurred (Table 1, entries 14 and 15). Finally, the presence of AgNO3 and AgOTf salts leads to the significant formation of 1a in 98 and 93% isolated yields, although 20 mol % was used in each case (Table 1, entries 19 and 20). These findings suggest that AgNPs with the size of <15 nm were found to catalyze the reduction process in the presence of NaBH4, within short reaction time and under mild conditions, results that are in good agreement with previous studies.21,22 On the basis of these findings, herein we attempt to combine—for the first time—the application of this simple catalytic system in the highly diverse and complex environment of the MCR chemical space, without the need of a protecting group, as well as into the facile one-pot synthesis of substituted 3,4-dihydroquinazolines, molecules with significant biological activity.

In order to determine if the present examined catalytic reduction processes can also be applicable to a variety of multifunctional nitro compounds, different starting materials were synthesized 1−7 and 8−10 and tested under the above two catalytic system, the Ag/HMS(10)−NaBH4 (Scheme 2).

To our surprise, the corresponding amine derivatives 1a−10a were formed as the only product, in high conversions (92−98%, based on nitro consumption, results not shown) as measured by 1H NMR from the crude reduction mixture and isolated yields in 84−95%, as shown in Scheme 2 (values in parentheses corresponds to the isolated yields under the Ag/HMS(10)−NaBH4 catalytic system). Interestingly, not only amine bonds but also other easily reducible moieties as chloro, aldehyde, or methyl ketone under the present conditions remained intact. These results support unambiguously the high catalytic activity of the used catalytic system Ag/HMS(10)−NaBH4 toward the chemoselective reduction of such multifunctional nitro derivatives to the corresponding amines.

On the basis of this outcome, the present research was extended to more complicated multifunctional nitro derivatives, such as substituted tetrazoles (11−20), bearing also the corresponding methylesters of the amino acids β-alanine, alanine, leucine, and valine for example compounds 16−20 (Scheme 3). Remarkably, the reduction processes using the Ag/HMS(10)−NaBH4 do not affect either the chemical functionality of the tetrazole ring or the chloro and methyl ester groups, giving the corresponding multifunctional amines (11a−20a) as the only products in high isolated yields (86−94%) and selectivity (>99%), after short reaction time (1−3 h). The measured diastereoselectivity (dr) of the amines 18a−20a corresponds to the initial ratio of the corresponding starting nitro compounds 18−20, as observed by 1H NMR (see Supporting Information). These results support further the high activity and chemoselectivity of the present catalytic system toward the nitro group reduction of a series of multifunctional biological active molecules, a facile and useful procedure plausibly applicable for a multi-gram-scale synthesis.

The synthetic value of the present reductive catalytic systems was verified by performing a one-pot C−N cyclization reaction of the in situ formed ortho-amino derivatives 21a−27a, forming a series of novel dihydroquinazolin-2-ones (21b−27b, Scheme 4). Dihydroquinazolin-2-ones are present in many bioactive compounds with anticancer36−38 and anti-inflammatory39 properties, as well as against neurological diseases.40 There are mainly three different synthetic
approaches; the majority of the dihydroquinaxolinone derivatives is accessed through an \(\sigma\)-halogen substituted nitro or aniline phenyl group and its subsequent reaction with amino acids\(^{37,39,41,42}\) or the reduction of quinoxaline derivatives through a transition metal-catalyzed asymmetric hydrogenation\(^{43−45}\) (Scheme 1). The aforementioned processes involve, on average, more than three sequential steps, protecting groups, Lewis acids and in many cases expensive starting materials. In addition to these two methods, few examples have been described in the literature with different approaches for example reactions of \(\sigma\)-phenylenediamine (oPDM) toward dihydroquinoxaline derivatives.\(^{35,36}\) Herein, a mild and efficient retrosynthetic scheme is proposed based on the above heterogeneous catalytic systems including the one-pot ring closing pathway of the in situ formed amine derivative (Scheme 4).

Thus, the Ag/HMS(10)—NaBH\(_4\)-catalyzed transfer hydrogenation process of the \(\sigma\)-nitro substituted multifunctional compounds performed toward to the corresponding amines (21a−27a) in 0.2 mmol reaction scale. In all cases, a direct formation of the corresponding cyclized products dihydroquinoxalino-2-one (21b−27b), through an intramolecular transamidation pathway (intramolecular C=N cyclization process), was observed by thin layer chromatography (TLC). It is worth noting that during the reaction pathway, a mixture mainly containing the cyclic and the starting amine was determined by \(^1\)H NMR of the crude reaction mixture (see Figure S2). It is also worth noting that this pathway was observed when the methyl carbamate group existed in the starting material structure (21−27), which is eliminated as glycine methyl ester (a good living group) under the intramolecular nucleophilic pathway. Finally, high isolated yields were measured in all cases (89−96\%) within a reaction time ranged between 5 and 12 h, results that support the clean and mild efficacy of the later heterogeneous catalytic process.

The observed retrosynthetic scenario is based on the facile MCR synthesis of the starting nitro compound by an Ugi-Smiles reaction of the readily available \(\sigma\)-nitrophenols, amines, aldehydes, and glycine methyl isocyanide in high yields (Scheme 4). The subsequently catalytic results shown in Scheme 4 indicated that the corresponding cyclized products (21b−27b) were formed in good to high isolated yields. This spontaneous in situ reduction-cyclization pathway occurred within short reaction time and under ambient conditions supports further the synthetic value of the present transfer hydrogenation reactions using Ag/HMS—NaBH\(_4\) as the heterogeneous catalytic systems. To the best of our knowledge, there is a study in the literature reported on the Ugi-Smiles
adduct transformation to the quinoxaline derivatives under hydrogenation conditions with Pd/C (10 mol %) as the catalyst and acidic conditions using p-toluenesulfonic acid.46 In all cases, prolonged reaction times and multistep workup protocols were required until the final product isolation; compared to the present heterogeneous, fast, mild, and lab-scale transfer hydrogenation process is catalyzed by AgNPs.

On the basis of these results, the Ag/HMS−NaBH4 catalytic system was further tested for possible lab-scale production of dihydroquinoxalin-2-ones from the corresponding multifunctional amines. For this reason, 1 mmol of the nitro derivative 22 was reduced in the presence of Ag/HMS 10% wt (20 mg, 1.8 mol %) with 2 mmol of NaBH4 in 6 mL MeOH/THF = 1:1. After completion of the reduction (ca. 120 min based on TLC analysis), 50 mg of silica gel was added into the reaction mixture and left under stirring for appropriate time (monitored by TLC) to afford the corresponding cyclized product 22b. After that, the mixture was filtered and the filtrate was evaporated under vacuum to afford, after chromatographic purification (see Experimental Section), the corresponding dihydroquinoxalin-2(1H)-one derivative 22b in pure forms with 78% isolated yield based on the corresponding nitro amount. This result corresponds to a high turnover number of 43, as measured from the ratio of product 22b (mmol)/supported Ag/HMS (mmol).

Moreover, our synthesis gives an easy access to inhibitors of the soluble epoxide hydrolase (sEH), an important target for therapies against hypertension or inflammation; demonstrating this potential, derivatives 21b and 22b were designed and accordingly synthesized with our protocol based on the cocrystallized compound 28 (PDB ID 3WKB), which was identified as a potent fragment (IC50 = 61 μM, LE = 0.32) of the aforementioned enzyme inhibition (Figure 1).38 To our delight, this is the first example in the literature that describes the synthesis in the lab scale of such heterocyclic molecules based on the present gold- or silver-based heterogeneous catalytic conditions.

**CONCLUSIONS**

In conclusion, we have demonstrated that silica-supported AgNPs can be applied to more complicated organic compounds, containing the highly diverse and complex environment of the MCR chemical space, and catalyze the selective reduction of a series of such multifunctional nitro-
compounds into the corresponding amines employing NaBH₄ as reducing agents. Among the tested catalytic systems, the Ag/HMS(10) with an average of AgNP size below 15 nm showed the best catalytic activity in terms of the conversion and selectivity of the amine formation. The catalyst was found to be highly chemoselective even for more complex molecules such as tetrazole and amino acid-substituted derivatives. The present Ag/HMS–NaBH₄ catalytic system represents an expeditious approach toward the production of the heterocyclic dihydroquinoloxalin-2-ones with good-to-high isolated yields, even to larger-scale, via the one-pot ring closing pathway based on the chemoselective reduction of the nitro group to the corresponding amine. The present heterogeneous catalytic procedure gives an easy access to synthesize inhibitors of the sEH for therapies against hypertension or inflammation.

■ EXPERIMENTAL SECTION

General. All the solvents and reagents were purchased from Sigma-Aldrich, Flurochem, Acros and were used without further purification. Thin layer chromatography was performed on silica gel plates (0.20 mm thick, particle size 25 μm). Nuclear magnetic resonance spectra were recorded on Agilent 500 (1H NMR (500 MHz), 13C NMR (126 MHz)). Chemical shifts for 1H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quint = quintet, dd = double of doublets, ddd = double doublet of doublets, m = multiplet. Mass spectra (HRMS) were determined on an electrospray ionization mass spectrometry (ESI-MS), by using a Thermo Fisher Scientific (Bremen, Germany) model LTQ-Orbitrap Discovery MS, at a flow rate of 10 μL/min using a syringe pump. The infusion experiments were run using a standard ESI source operating in a positive ionization mode. Source operating conditions were a 3.7 kV spray voltage and a 300 °C heated capillary temperature.

Preparation of Catalysts. The HMS mesoporous silica was synthesized based on previously reported methods. Dodecylamine (DDA), which was used as the mesostructure directing agent (template), was dissolved in ethanol followed by addition of water in a final ratio of water/ethanol = 80:20, v/v. Tetraethyl orthosilicate (TEOS), used as the silica source, was then added slowly, and the mixture was stirred for 30 min at room temperature followed by hydrothermal aging in sealed PP bottles, in a shaker bath, at 65 °C for 24 h. The white product was filtered, washed with water, and dried at room temperature and at 90 °C for 3 h. The reaction mole stoichiometry was 1TEOS/0.23DDA/9.0EtOH/95H₂O. The organic template was removed from the dried as-synthesized samples by calcination at 600 °C for 4 h in air.

The metallic silver (Ag)–supported catalysts were prepared by the method using amines as reductants. The precursor silver compound was as-synthesized silver oxide (from AgNO₃ and oxalic acid), which was solubilized in aqueous solution of ethylenediamine (65 vol %). The amount of silver oxide was adjusted so that the final silver loading of the catalysts to be 10, 30, or 50 wt % Ag/HMS. Aqueous solution of ethanolamine was then added to the ethylene diamine solution, followed by addition of HMS silica under continuous stirring at room temperature. The molar ratio of ethylenediamine and ethanolamine to Ag was equal to 3 and 0.5, respectively. The suspension formed was further left under stirring at room temperature for 1 h, after which the temperature was gradually raised up to 120 °C under vacuum in order to induce the reduction of silver (occurred at about 70–80 °C) and evaporate water and most of the amines. The collected paste was dried at 100 °C in air and was then calcined at 350 °C for 3 h in order to remove the residual organic compounds.

Physicochemical Characterization. The Ag content of the catalysts was determined by inductive coupled plasma–atomic emission spectroscopy using a Plasma 400 (PerkinElmer) spectrometer, equipped with a Cetac6000AT+ ultrasonic nebulizer. Nitrogen adsorption/desorption experiments at −196 °C were performed using an automatic volumetric sorption analyzer (Autosorb-1MP, Quantachrome). Powder X-ray diffraction (XRD) experiments were conducted on a Shimadzu XRD 7000 diffractometer using a Cu Kα X-ray radiation operating at 45 kV and 100 mA. TEM experiments were carried out in a JEOL 2011 high-resolution transmission electron microscope operating at 200 kV, with a point resolution of 0.23 nm and C₆ = 1.0 mm. SEM experiments were performed on a JEOL 6300 microscope.

Synthetic Procedure of the Nitro-Substituted MCR Compounds via the Ugi-Smiles Reaction. A solution of the corresponding aldehyde (5.0 mmol), nitro-substituted phenol (5.0 mmol), and amine (5.0 mmol) in methanol (5 mL) was stirred at room temperature for 15 min. Subsequently, isocyanide (5.0 mmol) was added and the reaction was stirred at room temperature for approximately 20 h. After reaction completion, monitored by TLC, the reaction mixture was concentrated in vacuo and the residue was purified by column chromatography using silica and eluent solvent, a mixture of hexane/ethyl acetate in a ratio from 5:1 to 1:3, affording the desired compounds 1–7 and 21–27 in good-to-high yields.

Synthetic Procedure of the Nitro-Substituted MCR Compounds via the Ugi-Tetrazole (UT-4CR) Reaction. A solution of the corresponding aldehyde or ketone (5.0 mmol) and amine or amino acid methyl ester (5.0 mmol) in methanol (5 mL) was stirred at room temperature for 15 min. Subsequently, isocyanide (5.0 mmol) and TMSN₃ (5.0 mmol, 665 μL) were added and the reaction mixture was stirred at room temperature for approximately 20 h. After reaction completion, monitored by TLC, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography using silica and eluent solvent, a mixture of hexane/ethyl acetate in a ratio from 5:1 to 1:5, affording the desired compounds 11–20 in high yields.

Synthetic Procedure of the Nitro-Substituted MCR Compounds via the Ugi-Four Component (U-4CR) Reaction. A solution of the corresponding aldehyde (5.0 mmol), carboxylic acid (5.0 mmol), and amine (5.0 mmol) in methanol (5 mL) was stirred at room temperature for 15 min. Subsequently, isocyanide (5.0 mmol) and TMSN₃ (5.0 mmol, 665 μL) were added and the reaction mixture was stirred at room temperature for approximately 20 h. After reaction completion, monitored by TLC, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography using silica and eluent solvent, a mixture of hexane/ethyl acetate in a ratio from 5:1 to 1:5, affording the desired compounds 8–10 in good-to-high yields.

General Catalytic Reduction of the Nitro-Substituted Derivatives to the Corresponding Amines 1a–27a. To a sealed tube containing the corresponding nitro-substituted compounds (0.2 mmol) in 0.5 mL of methanol and 0.5 mL of THF, NaBH₄ (0.4 mmol) and Ag/HMS, 10 % wt (1.4 mol %,
K2CO3 was used to accomplish the NMR spectra. Hydroquinoxalin-2(1H)-one derivatives 21b−27b. To a sealed tube containing the corresponding nitro compounds (0.2 mmol) in 0.5 mL of methanol and 0.5 mL of THF, NaBH4 (0.4 mmol) and Ag/HMS, 10% wt (1.4 mol %, 3 mg), were added. The reaction mixture was stirred at room temperature for the appropriate time, and it was monitored by TLC. After that, the slurry was filtered to remove the catalyst and the residue was washed with methanol (~5 mL). The filtrate was evaporated under vacuum to afford, after chromatographic purification as described above with hexane/ethyl acetate from 30:1 to 2:1 as the eluent, the corresponding dihydroquinoxalin-2(1H)-one derivatives 21b−27b in pure forms.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02749.

Physicochemical characteristics of HMS mesoporous silica and 50% w/w Ag/HMS; TEM and SEM images; and copies of 1H, 13C, and NOESY-1D NMR spectra of the products (PDF)

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**Author Contributions**

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**Notes**

The authors declare no competing financial interest.

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