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Additional Information

Diastereoselective synthesis of Pyranoquinolines over Zr-containing UiO-66 Metal Organic Frameworks

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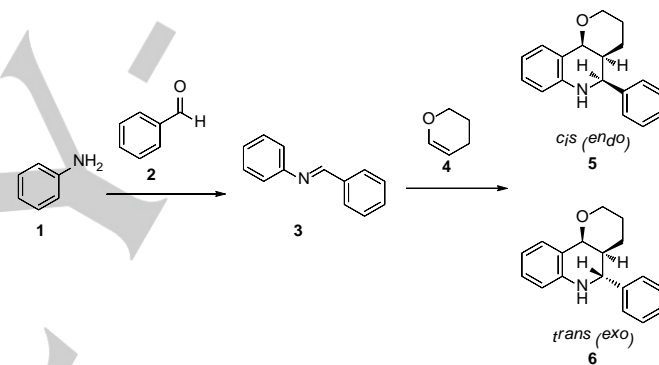
Abstract: Zr-terephthalate MOFs UiO-66 and UiO-66-NH₂ are found to be highly diastereoselective catalysts for the synthesis of pyrano[3,2-c]quinolines through an inverse electron-demand aza-Diels-Alder [4+2] cycloaddition of an aryl imine (formed in situ from aniline and an aldehyde) and 3,4-dihydro-2H-pyran in one pot, affording the corresponding *trans* isomer in 90-95% diastereomeric excess. The solids are stable under the reaction conditions and can be reused at least three times without significant loss of activity or diastereoselectivity.

Introduction

Metal Organic Frameworks (MOFs) are crystalline porous materials constructed by metal ions or metal oxo-clusters connected through multitopic organic ligands into extended mono-, bi- or tridimensional frameworks. Their strictly regular and tunable pore system and huge surface areas of thousands of square meters per gram, together with the possibility to introduce different functionalities at the metal nodes, at the organic linkers, or inside the pores (either by direct synthesis or through post-synthesis modification of pre-formed MOFs), make them very promising candidates for applications in gas separation,^[1-3] and heterogeneous catalysis,^[4-7] among others. In particular, the high tunability of composition, structure and intracavity chemical environment attainable with MOFs are valuable tools for the design synthesis of highly chemo-, regio- and enantioselective MOFs to be used as catalysts for the synthesis of high added value chemicals.

Tetrahydroquinoline derivatives are an important class of heterocyclic compounds with a wide variety of biological activities, such as anti-allergic,^[8] anti-inflammatory,^[9] anti-arrhythmic,^[10] anti-malarial,^[11] anti-tumor^[12] or anti-oxidant.^[13] Among them, pyrano[3,2-c]quinolines (hereafter PQs) are the core of various natural bioactive alkaloids, such as simenoline, huajiasimuline, flindersine, veprisine or oricine.^[14, 15] In our ongoing research to apply metal organic frameworks (MOFs) as heterogeneous catalysts for the synthesis of high added value chemicals, we have recently reported that (tetrahydro)quinoline derivatives can be readily prepared by using bifunctional heterogeneous catalysts based on Pd or Pt species encapsulated inside Cr-MIL-101 MOFs, through a tandem

nitroarene reduction and intramolecular reductive amination of nitrocinamaldehyde.^[16] Nonetheless, one of the most important synthetic routes for preparing six-membered nitrogen heterocycles, including (tetrahydro)quinolines, is the so-called Povarov reaction.^[17] This reaction consists of an inverse electron-demand aza-Diels-Alder [4+2] cycloaddition of an aryl imine (formed in situ from aniline and an aldehyde) and electron-rich alkenes. In particular, by using 3,4-dihydro-2H-pyran (hereafter DHP) as electron-rich dienophile, the corresponding PQs are obtained, usually as a pair of *cis* and *trans* diastereoisomers, the ratio of them depending on the synthesis conditions used:



Various homogeneous and heterogeneous acid catalysts, including SnCl₂,^[18] SbCl₃ doped on hydroxyapatite (SbCl₃-HPA),^[19] tungstophosphoric acid supported on nano sized MCM-41 (TPA/MCM-41),^[20] perchloric acid adsorbed on silica gel (HClO₄-SiO₂),^[21] GdCl₃,^[22] or ferric sulfate,^[23] have been reported for the synthesis of pyranotetrahydroquinolines. However, some of the methods used so far suffer from limitations such as the use of large catalyst amounts (up to 50 mol%), very low diastereoselectivities, or poor catalyst reusability. Herein we will show that Zr-containing MOFs bearing acid sites can be efficiently used as recoverable heterogeneous acid catalysts for the synthesis of PQs, affording high activities and excellent diastereoselectivities to the *trans* (exo) isomer, 6. In related precedents to the present work, some authors have indeed demonstrated that various MOFs bearing acid functionalities can catalyze Diels-Alder reaction (both normal and inverse-demand) of various substrates.^[24-29]

In the present work, we have considered the use of Zr-containing MOFs of the UiO-66 type to catalyze the synthesis of PQs. These MOFs belong to a highly robust family of compounds formed by Zr₆ hexameric oxo-aggregate units connected by 12 linear dicarboxylate molecules in a close cubic packing, thereby defining octahedral and tetrahedral pores, both of them accessible through triangular windows with free openings of about 6 Å (in the case of UiO-66 with terephthalate linkers), as shown schematically in Figure 1.^[30] However, this

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ideal structure of UiO-66 type MOFs is frequently interrupted by the occurrence of defects, mainly associated to linker deficiencies, that leads to a connectivity of the Zr_6 units lower than the expected value of 12, and to the formation of Zr^{4+} ions having coordinative unsaturation.^[31] There are now clear evidences that coordinatively unsaturated Zr^{4+} sites associated to defects are the main responsible for the well know acid character of these compounds, as it has already been shown for a number of acid catalyzed reactions.^[32-35]

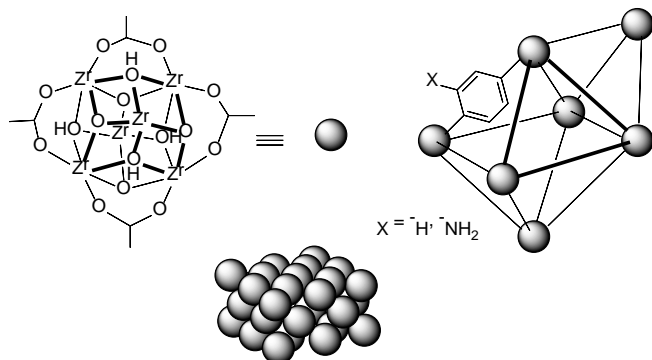


Figure 1. Pictorial view of the UiO-66 MOF structure showing the Zr_6 oxo-aggregates (*left*) and their close cubic packing (*center*) forming octahedral and tetrahedral cavities (*right*), both of them accessible through triangular faces (evidenced by bold lines).

Results and Discussion

Synthesis of PQs over Zr-MOFs.

When an acetonitrile solution of aniline, benzaldehyde and DHP was contacted with the Zr-containing UiO-66 type MOFs (3.6 mol% Zr with respect to aniline), the imine intermediate **3** was immediately obtained, and was gradually converted into the desired *cis* and *trans* PQs **5** and **6**. As an example, Fig. 2 shows the kinetic evolution of products obtained when UiO-66 was used as catalyst. Thus, after 22 h of reaction time, the final yield of PQ obtained was 83%, with an excellent diastereoselectivity; the *trans*:*cis* diastereomeric excess (d.e.) of 94% (as determined by 1H NMR). Besides PQ and the intermediate imine, a minor side product (below 5% yield) was also detected, which was identified as the aza-Michael addition product of aniline and DHP. When acetonitrile was replaced by other solvents, either polar (ethanol, *N,N*-dimethylformamide) or apolar (toluene, hexane, chloroform), the final yield of the PQ product was considerably lower or even negligible. As expected, no PQ was obtained in the absence of catalyst. Table 1 summarizes the results obtained with various MOFs and other acid catalysts taken from the literature for comparison.

According to the XRD and ICP-OES analysis of the solid catalyst recovered after the reaction (see Fig. S1 in the Supporting Information), UiO-66 was found to be stable under the reaction conditions and was reusable for at least three catalytic cycles without significant loss of activity or diastereoselectivity (entries 1-3).

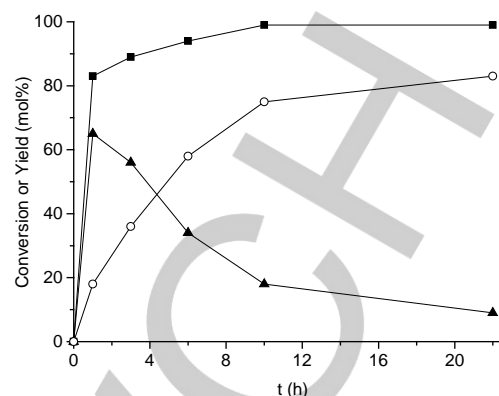


Figure 2. Conversion of aniline **1** over UiO-66 (*closed squares*) and evolution of products: intermediate imine **3** (*closed triangles*) and PQs **5** and **6** (*open circles*).

Table 1. Synthesis of PQs over various solid acid catalysts.^a

	Catalyst	Catal. (mol%)	Time (h)	PQ yield (mol%)	d.e. ^b (%)
1	UiO-66	3.8	10 (22)	75 (83)	94
2	UiO-66 1 st reuse	3.8	22	77	92
3	UiO-66 2 nd reuse	3.8	22	75	91
4	UiO-66-NH ₂ (45 nm)	3.8	3(10)	74 (88)	88
5	UiO-66-NH ₂ (60 nm)	3.8	3 (22)	32 (77)	90
6	UiO-66-NH ₂ (130 nm)	3.8	22	<5	-
7	ZrCl ₄	3.8	0.25	85	46
8	(Cr)-MIL-101	3.8	24	<5	-
9	(Al)-MIL-101-NH ₂	3.8	24	<5	-
10	(Fe)-MIL-101-NH ₂	3.8	24	<5	-
11	SnCl ₂ ·2H ₂ O ^[16]	10	1.8	95	40
12	SbCl ₃ -HAP ^{[19],c}	1.6	2.5	85	100
13	TPA/MCM-41 ^[20]	0.5	2.25	88	16
14	HClO ₄ -SiO ₂ ^[21]	5	0.25	95	78
15	GdCl ₃ ^[22]	25	12	84	22
16	Fe ₂ (SO ₄) ₃ ·xH ₂ O ^{[23],c}	10	1.5	87	56
17	NbCl ₅ ^[36]	10	0.5	85	90
18	Sml ₂ ^[37]	20	5	88	46
19	InCl ₃ ^[38]	20	0.5	80	18
20	LiBF ₄ ^[39]	20	1.5	88	70
21	CuBr ₂ ^[40]	50	2	76	58

^a Reaction conditions with the Zr-MOF catalysts: Aniline (1 mmol), benzaldehyde (1.2 mmol) and DHP (2 mmol) in acetonitrile (0.5 mL), Zr-MOF (3.8 mol% Zr) at room temperature. ^b Diastereomeric excess: $[(trans-cis)/(trans+cis)] \times 100$. ^c The reaction was carried out at reflux temperature (acetonitrile solvent).

As compared with UiO-66, UiO-66-NH₂ afforded slightly better results in terms of PQs yield in shorter reaction time (see entry 4 and Fig. S3 in Supporting Information), while affording also excellent diastereomeric ratios. UiO-66-NH₂ was also found to be stable and reusable without loss of activity under the reaction conditions used. In comparison, ZrCl₄ (entry 7) was

found to be much more active for the aza-Diels-Alder reaction than both Zr-MOFs, yielding 85% PQ in only 30 min under the same reaction conditions. However, the product was obtained as a mixture of *trans* and *cis* isomers of 73:27, corresponding to a considerably lower diastereomeric excess of only 46%.

To put into context the results obtained with the Zr-MOFs, we also compared our catalytic results with other solid catalysts described in the literature. In particular, concerning diastereoselectivity, the Zr-MOFs rivaled with the results obtained with NbCl_5 and $\text{HClO}_4\text{-SiO}_2$, and were clearly surpassed only by $\text{SbCl}_5\text{-HAP}$ (entry 12). However, besides these exceptions, Zr-MOFs largely outperformed most of the solid acid catalysts reported so far in the literature. Altogether, considering the good activity, the excellent diastereoselectivity and the easy reusability, the Zr-containing MOFs studied in the present work emerge as convenient and reusable solid acid catalysts to carry out the room temperature synthesis of PQs from amine, aldehyde and DHP in one pot with excellent diastereoselectivity.

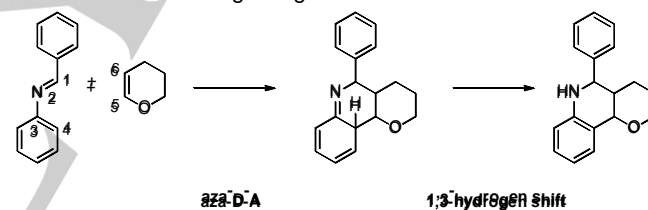
Considering the dimensions of PQs relative to the pore openings of the Zr-MOFs, it is evident that the Povarov three-component coupling reaction can only take place at the external surface of the solid catalyst. In agreement with this, three different UiO-66- NH_2 samples with particle sizes ranging from 45 nm to 130 nm (see Fig. S2 in the Supporting Information) showed significant differences in catalytic activity, decreasing in the order of increasing particle size, as expected. Thus, the turnover frequency (TOF) for the formation of PQ calculated after 3 h of reaction was 6.5 h^{-1} for the sample with the smallest particles (45 nm). This value was less than half when we used a sample containing particles of 60 nm on average (2.8 h^{-1}), while a UiO-66- NH_2 sample with particles of 130 nm was almost inactive for the formation of PQ (compare entries 4-6 in Table 1). If only simple geometric considerations (surface-to-volume ratio) are taken into account, one would expect much smaller differences in the catalytic activity of the samples with 45 nm and 60 nm particles, of around 33%. Therefore, the higher activity of the sample with the smallest particles probably reflects a higher amount of defects (in the form of linker deficiencies) located at the external surface as compared to the sample with particles of 60 nm. It is worth mentioning that the analysis of the thermogravimetric curves of the samples can provide an estimation of the overall amount of linker defects (both internal and external), following the method proposed by Valenzano et al.^[31]. Therefore, since we did not observe significant differences in the total amount of defects of these two samples (around 8% in both cases), our catalytic results suggest that these defects are not equally distributed among internal and external surfaces of the MOFs from one sample to another (see Table S1 and discussion therein).

In order to circumvent product diffusion limitations occurring when narrow pore Zr-MOFs are used as catalysts, we turned to metal organic compounds with pores in the mesoporous range. In particular, we considered trivalent metal terephthalates of the MIL-101 family. This is a family of highly robust compounds featuring mesoporous cavities (~3-3.5 nm) accessible through pentagonal and hexagonal windows of 1.2-

1.5 nm, which are large enough to allow diffusion of very large molecules. Moreover, these materials are known to exhibit Lewis acid properties arising from coordinative unsaturation of the trivalent cations in the MIL-101 structure, which in principle could also catalyze the Povarov reaction leading to PQs. However, when these MIL-101 materials were used as catalysts, there was hardly any PQ formation (maximum yields below 5-10%) under the mild reaction conditions used (room temperature and only 3.8 mol% M^{3+} with respect to aniline). This result probably reflects the lower polarizing power (Z^2/r ratio), and thus, the lower Lewis acidity of Fe^{3+} , Cr^{3+} and Al^{3+} cations with respect to the Zr^{4+} ions present in UiO-66 type compounds. Therefore, at the light of our catalytic results, Zr^{4+} ions (with coordinative unsaturation due to ligand defects in the structure^[33]) are strong enough to activate the intermediate imine, thus increasing the electrophilic character of the carbonyl carbon (coming from benzaldehyde) and facilitating the attack of the electron-rich DHP dienophile. On the contrary, M^{3+} ions in MIL-101 would not be capable of activating enough the intermediate imine to trigger the Diels-Alder cycloaddition at room temperature.

Proposed mechanism

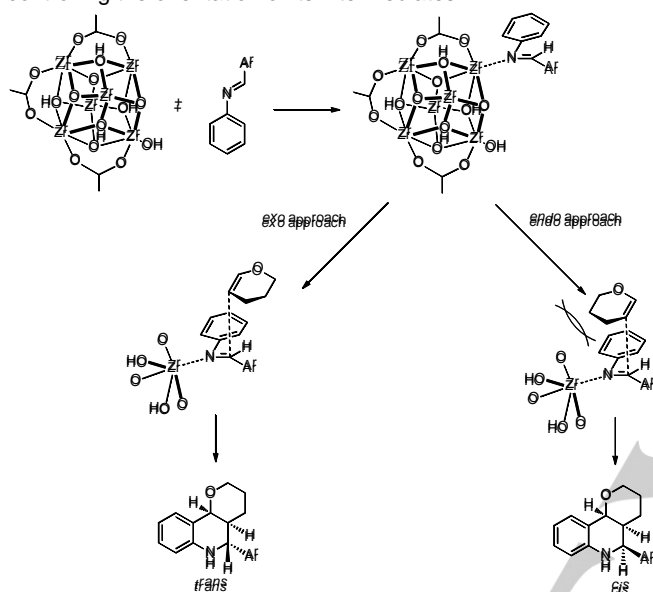
The Povarov reaction leading to PQs is actually a domino two-steps reaction consisting of an aza-Diels-Alder [4+2] cycloaddition (aza-D-A), followed by a 1,3-hydrogen shift tautomersim to yield the final tetrahydroquinoline molecule, in which the aromatic ring is regenerated:



There is still some controversy on the mechanism of the aza-D-A reaction, on whether it is a concerted or a stepwise reaction.^[36, 41, 42] It is generally accepted that the use of strong electrophilically activated azadienes and strong nucleophilically activated ethylenes favors a two-step reaction. Activation of the azadiene can either be achieved by protonation of the imine by Brønsted acids or by coordination of the N atom to strong Lewis acids, while the presence of electron-releasing groups in the ethylene increases its nucleophilic character. The first step consists in the nucleophilic attack from C6 carbon of the ethylene to C1 carbon of the imine (the attack to C4 carbon being very energetically unfavorable). This C1-C6 single bond formation can take place along two approaching directions (*endo* and *exo*), which will finally determine the formation of either *cis* or *trans* PQ isomers. The second step of the aza-D-A consists in the ring closure reaction by formation of the C4-C5 single bond.

In the particular case of the Povarov reaction catalyzed by Zr-MOF, the following mechanism can be hypothesized. In a first step, the *in situ* formed imine is coordinated to the coordinatively unsaturated Zr ions of the MOF, most probably associated to missing linker defects. This coordination activates the electrophilic character of the imine, thus favoring the nucleophilic

attack by DHP. The presence of bulky substituents in the Lewis acid coordinated to the imine can introduce important steric hindrance, which would favor the formation of the *trans* isomer through the *exo* approach of the DHP molecule. In this sense, the MOF can be considered as a "macroligand" of the Zr ions, which would explain the high diastereomeric selectivity observed. A similar mechanism has been proposed by da Silva et al. to explain the diastereoselectivity of the NbCl₅ catalyzed Povarov reaction,^[36] while steric hindrance has also been claimed as the responsible factor influencing the outcome of a reaction by controlling the orientation of its intermediates.^[43]



Once the aza-D-A product has been formed, the ensuing 1,3-hydrogen shift reaction takes place, leading to the final PQ product. Again, this reaction can be considered either a concerted or a stepwise process. However, the direct 1,3-hydrogen shift is very unfavorable due to the formation of a very strained four member transition state.^[41] Given the acid character of the H involved in the tautomerization, the presence of a basic species or protic solvents (such as water) is expected to accelerate the reaction. Therefore, the presence of amino groups in UiO-66-NH₂ can be responsible for the higher catalytic activity observed with respect to UiO-66, by either participating directly in the tautomerization reaction, or by favoring the adsorption of water generated during the imine formation in the close proximity of the Zr catalytic sites. In this sense, it has been reported by Walton and co-workers that amino groups in the terephthalate linkers favors water adsorption on the material.^[44]

Conclusions

In this work we have shown that UiO-66 type Metal Organic Frameworks, containing coordinatively unsaturated Zr⁴⁺ ions associated to linker vacancies, are highly diastereoselective heterogeneous catalysts for the inverse electron-demand hetero-Diels-Alder cycloaddition (Povarov reaction) of imines

and DHP leading to *trans* pyrano[3,2-*c*]quinolines, with diastereomeric excess of ca. 90-95%. This diastereoselectivity clearly outperforms most of the solid Lewis acid catalysts reported so far, with the sole exception of SbCl₃-HAP.^[19] Both, UiO-66 and UiO-66-NH₂ compounds, made with terephthalic and aminoterephthalic ligands respectively, are stable under the very mild reactions conditions used (room temperature) and can be reused at least 3 times without significant loss of activity or diastereoselectivity.

The relatively narrow pores of UiO-66 materials with respect to the PQs dimensions prevent the reaction from occurring inside the pores of the MOF, so only the active centers located at the external surface of the particles contribute to the observed activity. Accordingly, as the average particle size of UiO-66-NH₂ increases from 45 to 60 nm, the calculated TOFs fall from 6.5 h⁻¹ to 2.8 h⁻¹.

Experimental Section

Synthesis of UiO-66 and UiO-66-NH₂. All syntheses were performed according to the procedure reported by Kandiah et al.^[45] Briefly, 750 mg of ZrCl₄ and either 740 mg of terephthalic acid (UiO-66) or 800 mg of aminoterephthalic acid (UiO-66-NH₂) were dissolved in 90 mL of DMF (Zr:ligand:DMF molar ratio of 1:1:220) and the solution was kept in a closed round bottom flask in an oil heating bath at 80 °C for 12 h without stirring, followed by another 24 h at 100 °C. The resulting materials were recovered by filtration and washed thoroughly with fresh DMF. Then the solids were washed three times by soaking them in dichloromethane for 3 h. Finally, the solid was recovered by filtration and dried under vacuum at room temperature. X-ray diffraction (Phillips X'Pert, Cu K α radiation) was used to confirm the expected structure type and high crystallinity of the materials.

Catalytic studies. In a typical catalytic reaction, 1 mmol of aniline (93 mg), 1.2 mmol of benzaldehyde (127 mg) and 2 mmol of 3,4-dihydro-2H-pyran (168 mg) in 0.5 mL of acetonitrile were contacted at room temperature with the MOF (3.6 mol% Zr with respect to aniline) in a 3 mL batch reactor with a magnetic stirrer. Reaction progress was monitored by GC (Varian 3900 with 30 m x 0.25 mm BS5-SGE column) and GC-MS (Agilent 6890 with 30 m x 0.25 mm HP-5 column and Agilent mass selective detector 5973) using dodecane as internal standard. After each cycle, the solid catalysts were recovered by centrifugation and Soxhlet washed overnight with acetonitrile and dried at 60°C before reuse. The crystallinity of the recovered material was determined by XRD and compared with that of the fresh material. The diastereisomeric excess of the products was determined by ¹H-NMR (Variant Unity 300 Plus Gemini at 300 MHz, in CDCl₃) from the integrated intensity of the peaks at δ 3.65 (td, *J* = 11.5, 2.5 Hz, 1H) for the *trans* isomer and δ 3.36 (td, *J* = 11.3, 2.9 Hz, 1H) and δ 5.33 (d, *J* = 5.6 Hz, 1H) for the *cis* isomer of the reaction crude spectrum.

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Keywords: Metal Organic Frameworks • Heterogeneous catalysis • Povarov reaction • Three-component coupling reactions • Pyranoquinoline synthesis

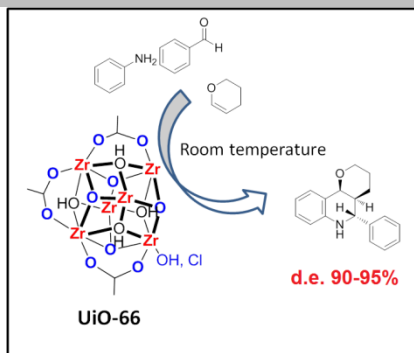
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Layout 1:

FULL PAPER

Zr-containing UiO-66 type compounds catalyze the Povarov reaction at room temperature, leading to *trans* pyrano[3,2-*c*]quinolines, with diastereomeric excess of 90-95%. The solids are stable and reusable without significant loss of activity or diastereoselectivity

**MOF catalysts***

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Diastereoselective Synthesis of Pyranoquinolines over Zr-containing UiO-66 Metal Organic Frameworks