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To be cited as: *Chem. Eur. J.* 10.1002/chem.201904095

Link to VoR: http://dx.doi.org/10.1002/chem.201904095

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DOI: 10.1002/chem.201xxxxxx

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Synthesis of 2-Arylisoindoline Derivatives Catalyzed by Reusable 1,2,4-Triazole Iridium on Mesoporous Silica through Cascade Borrowing Hydrogen Strategy

Wei Yao[a], Chenyang Ge[a,b], Yilin Zhang[c], Xiao-Feng Xia[a], Long Wang*[b], and Dawei Wang*[a]

Abstract: A new type of 1,2,4-triazole iridium complex and covalent attachment to mesoporous MCM-41 generated heterogeneous catalyst was found to be effective catalysts to the synthesis of 2-arylisoindolines, quinolines, cyclic amines and symmetrical secondary amines through cascade borrowing hydrogen strategy. Interestingly, the supported heterogeneous iridium catalyst, which was prepared from 1,2,4-triazole iridium complex and mesoporous MCM-41, exhibited high catalytic activity in the preparation of 2-arylisoindoline derivatives and symmetrical secondary amines. The catalyst system is good recyclable for at least five times. Besides the important effect of triazole, iridium sites grafted on siliceous supports, which could be able to act as multifunctional catalytic centers, and thus greatly enhanced catalytic activity of catalysts. Furthermore mechanistic experiments revealed that the reactions is initiated by an initial alcohol dehydrogenation and promoted by iridium hydride intermediate. Importantly, the direct detection of a diagnostic iridium hydride signal confirmed that the synthesis of 2-arylisoindolines is undergoing borrowing hydrogen process. This work provided an efficient example of isoindolines synthesis through borrowing hydrogen strategy.

Introduction

Derivatives of isoindolines were isolated much later than most of other heterocyclic compounds containing nitrogen, but this couldn't hinder the scientists' research interest and expanding application scope of isoindolines due to their broad biological activity, like anxiolytic, antipsychotic, anticonvulsive or anaesthetic activities.[1] Several isoindolines were known as ciritical antihypertensive drugs against cardiorenal diseases due to their nonsteroidal anti-inflammatory activity,[2] which significantly encouraged medicinal and organic chemists to acheive continous progress in this field.[3] A great number of isoindoline derivatives were isolated or synthesized during the past several decades for the discovery of their unknown biological properties and novel applications. Conventional reagents employed in the synthesis of isoindolines included strong bases, methylaluminoxane, titanium tetrachloride, butyllithium etc.[4] However, there has been lack of mild and economical approach to afford isoindolines, especially, using recyclable catalyst, mild conditions or solvent-free conditions. The synthesis of isoindoline derivatives from the simple amines and alcohols through borrowing hydrogen strategy has received considerable attention for providing an economically, environmentally friendly method to achieve the conventional alkylation of amines.[5]

Borrowing hydrogen methodology, also called hydrogen auto-transfer reaction, has become an effective tool in medicinal chemistry and organic synthesis area.[6,7] This methodology could provide convenient route to an abundance of pharmaceuticals and natural compounds from the very simple amines and alcohols. Under the conditions of the "borrowing hydrogen" methodology, alcohols are easily converted *in situ* into aldehydes or ketones, which are more reactive than alcohols and easily react with amines.[8,9] Recently, scientists described that N-arylpyrrolidine derivatives could be prepared from aniline and alcohols through transition metal catalysts in high yields. The synthesis of N-arylpyrrolidines provided a useful idea and ideal pathway for the development of isoquinoline compounds.[10] Based on the previous work on borrowing hydrogen area,[11,12] we envisioned that the synthesis of 2-arylisoindolines through cascade borrowing hydrogen reaction is also possible. The proposed new synthetic protocol based on cascade borrowing hydrogen strategy was shown in Scheme 1.

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[**] We gratefully acknowledge financial support of this work by the National Natural Science Foundation of China (21776111), the Fundamental Research Funds for the Central Universities (JUSRP 51627B) and MOE & SAFEA for the 111 Project (B13025).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201xxxxxx.

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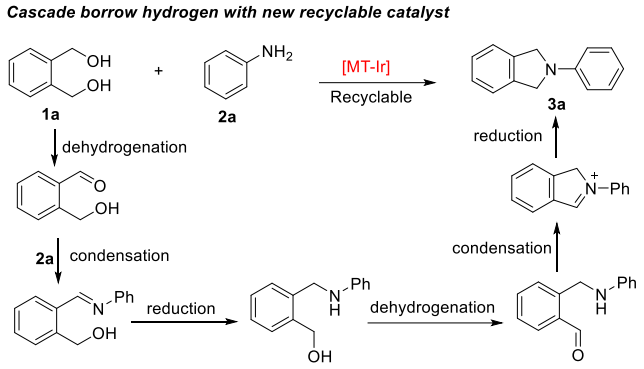
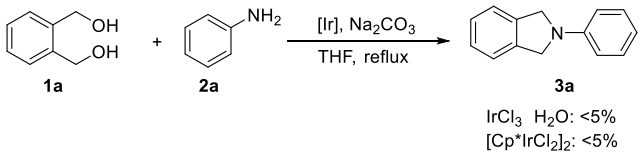


Scheme 1. The proposed new synthetic protocol through cascade borrowing hydrogen.

Recently, we synthesized several bisbenzoxazolyl and benzothienyl iridium(III) complexes, which exhibited good catalytic activity in borrowing hydrogen reaction of simple amines with alcohols, ketones with alcohols and alcohols with alcohols.[11] However, these novel complexes as well as other common iridium complex revealed no activity in the synthesis of isoindoline derivatives (Scheme 2). In this paper, we reported a new type of 1,2,4-triazole iridium complex and covalent attachment to mesoporous MCM-41 generated heterogeneous catalyst (MT-Ir), which are effective catalysts to the synthesis of 2-arylisoindoline derivatives, cyclic amines, quinolines and symmetrical secondary amines. Interestingly, the supported heterogeneous catalyst exhibited high catalytic activity in the preparation of 2-arylisoindoline derivatives. The recycling experiment showed that the structure of recovered catalyst maintained a high catalytic efficiency after five times.



Scheme 2. The new attempts.

2. Results and Discussion

2.1. The synthesis of mesoporous silica supported iridium catalyst (MT-Ir).

To better display superior catalytic performance of heterogeneous catalysts,[13] we next synthesize new type of heterogeneous triazole iridium catalysts to explore isoindolines synthesis. First, 1,2,4-triazole iridium (TA-Ir) was prepared from 1,2,4-triazole and iridium chloride under mixed solvents (2-ethoxyethanol/H_2O = 3:1). Next, 1,2,4-triazole iridium (TA-Ir) and (3-aminopropyl) triethoxysilane were mixed and stirred in a Schlenk tube under N_2 atmosphere to form (3-aminopropyl) triethoxysilane modified 1,2,4-triazole iridium complex (TAAT-Ir). According to literature,[14] mesoporous silica supported iridium catalyst (MT-Ir: M for MCM-41, T for TAAT) could be synthesized by using the reaction of TAAT-Ir and MCM-41 in MeOH (see supporting information for details).

2.2. Characterization of MT-Ir catalyst.

Scanning electron microscopy (SEM) images were first carried out. As shown in Fig. 1 (a) and (b), SEM images of the MCM-41 presented reunion shape and its appearance was spherical, whereas MT-Ir showed numerous lamellar crystals. Transmission electron microscopy (TEM) images clearly revealed that MT-Ir particles existed on the mesoporous MCM-41 (Fig. 1 (c) and (d)). Thermogravimetric curve of MT-Ir revealed that this catalyst could keep good thermal stability until 350 °C, which was consistent with the decomposition of TA-Ir. This implied that TA-Ir part was effective loaded on the mesoporous MCM-41 (see supporting information for details).

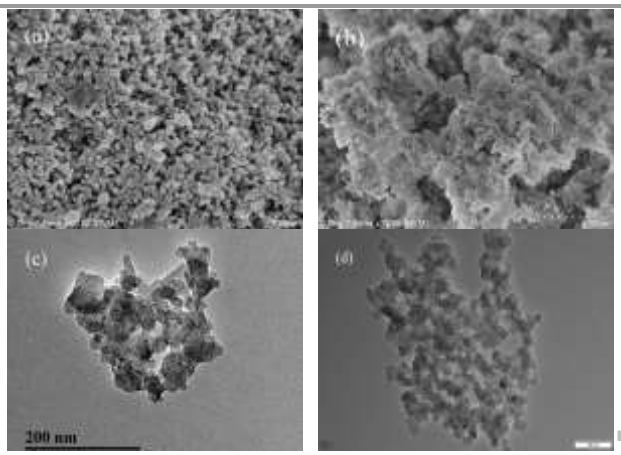


Fig. 1. (a): SEM image of the pure MCM-41; (b): SEM image of the catalyst MT-Ir; (c) and (d): TEM images of the catalyst MT-Ir.

In addition, energy dispersive X-ray (EDX) was performed and it showed that iridium, nitrogen and chlorine existed in MT-Ir (Fig. 2).

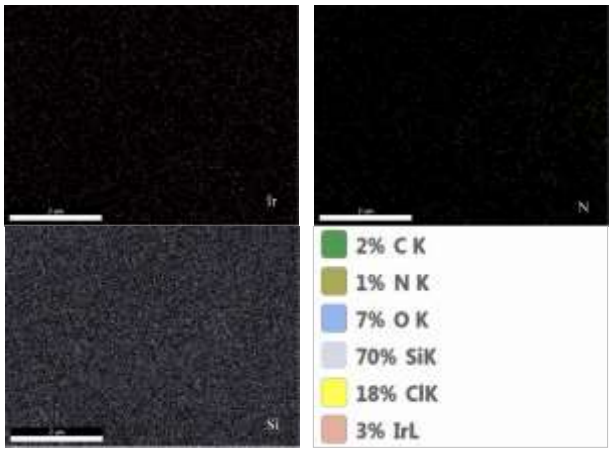


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Fig. 2. EDS images of the catalyst MT-Ir.

X-ray power diffraction (XRD) was also conducted to verification structure. The steamed bun peaks at 2θ = 5.81° of XRD pattern (b) was characteristic peaks of silica, which was reported in previous studies. Meanwhile the peak at 2θ =17.68°, 30.49°, 52.00° of XRD pattern (a) was peaks of iridium complex. The results revealed that 1,2,4-triazole iridium complex were well loaded on the MCM-41 (Fig. 3).

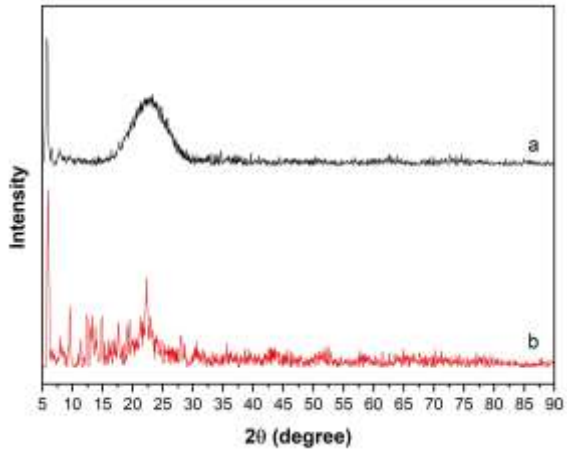
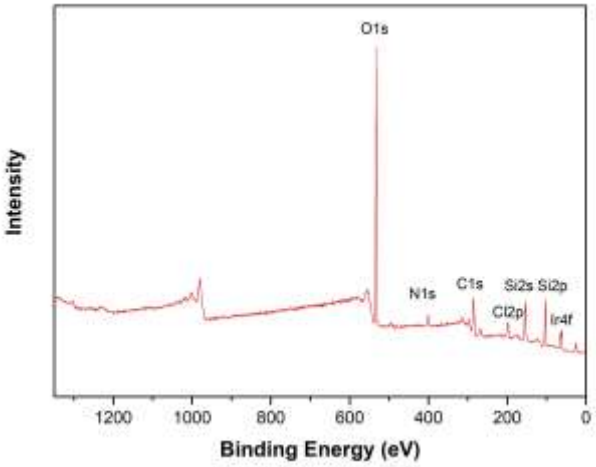


Fig. 3. XRD pattern of MCM-41 (a) and MT-Ir (b).

The element compositions and surface chemical states of MT-Ir composite were also proved by X-ray photoelectron spectroscopy. The obvious and wide XPS spectra indicated the presence of C, O, N, Si and Ir elements. The binding energy at 65.3 and 62.1 eV belonged to Ir3+ (Figure 4).



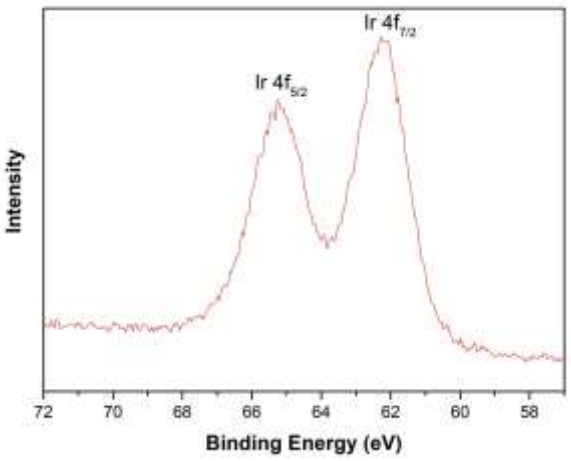


Fig. 4. XPS spectra of MT-Ir.

Furthermore, nitrogen sorption analysis was carried out. As shown in Fig. 5, the catalyst displayed a type IV isotherm and H_1 hysteresis loop, which are typical for mesoporous materials. A great decrease in surface area was observed for MT-Ir with respect to MCM-41 (from 1908.1 to 368.5 m^2/g). In comparison with the MCM-41, the surface area of the MT-Ir was greatly decreased, which indicated that the 1,2,4-triazole iridium complex (TA-Ir) was entered the channels of MCM-41, and had a significantly impactedthe catalyst pore structure.

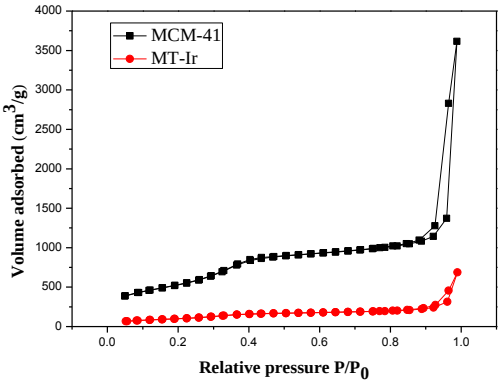


Fig. 5. N_2 sorption analysis for the MCM-41 and MT-Ir.

2.3. Catalytic Activity.

After preparation and characterization, the MT-Ir catalyst was applied to the synthesis of isoindoline from 1,2-phenylenedimethanol and aniline to investigate its catalytic activity. To our delight, the reaction could produce 37% yield of desired product after 24 hours (Table 1, entry 1). Subsequently, various bases such as cesium carbonate, sodium bicarbonate, triethylamine, sodium carbonate were examined and the best yield was obtained when cesium carbonate was used in this transformation. No reaction was observed when other iridium catalysts were used (Table 1, entries 9-13). It should be noted that when only MCM-41 or TA-Ir employed, lower product yields were seen (Table 1, entries 14-15). It was observed that the homogeneous catalyst (TAAT-Ir) could also produce

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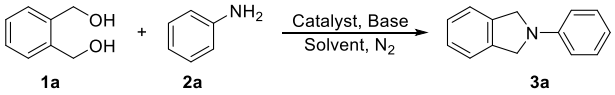
moderate yield of desired product (entry 19).

Table 1. Optimization of reaction conditions[a,b]



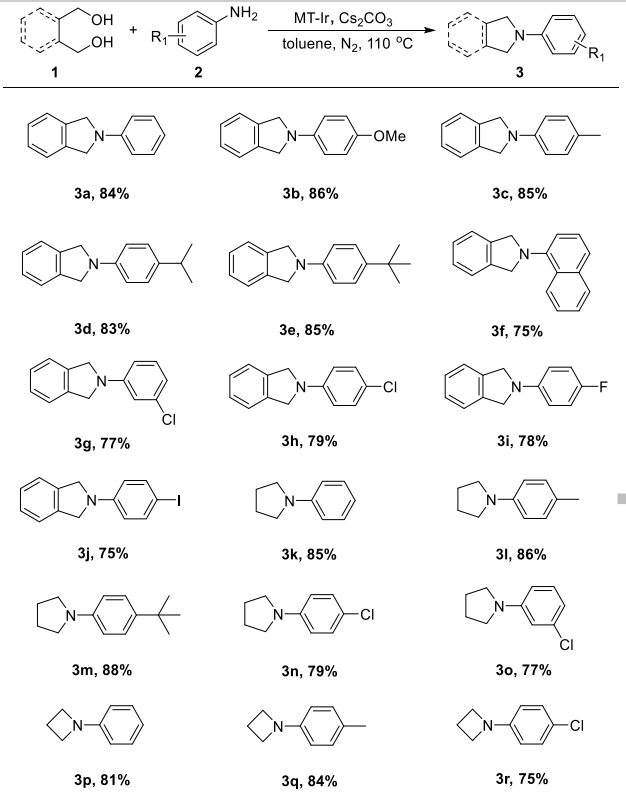
1a 2a 3a

Entry	Catalyst	Base	Solvent	Yield[%]
1	MT-Ir	KO*t*Bu	toluene	37 [c]
2	MT-Ir	$NaHCO_3$	toluene	<5 [c]
3	MT-Ir	KOH	toluene	63 [c]
4	MT-Ir	Cs_2CO_3	toluene	68 [c]
5	MT-Ir	Na_2CO_3	toluene	25 [c]
6	MT-Ir	NEt_3	toluene	<5 [c]
7	MT-Ir	Cs_2CO_3	toluene	84
8	-	Cs_2CO_3	toluene	<5
9	$IrCl_3$	Cs_2CO_3	toluene	<5
10	**A**	Cs_2CO_3	toluene	<5 [d]
11	**B**	Cs_2CO_3	toluene	<5 [d]
12	**C**	Cs_2CO_3	toluene	<5 [d]
13	TA-Ir	Cs_2CO_3	toluene	32
14	MCM-41	Cs_2CO_3	toluene	11
15	MT-Ir	Cs_2CO_3	dioxane	56
16	MT-Ir	Cs_2CO_3	EtOAc	<5
17	MT-Ir	Cs_2CO_3	Et_2O	<5
18	MT-Ir	Cs_2CO_3	MeOH	<5
19	TAAT-Ir	Cs_2CO_3	toluene	61%

[a] Reagents and conditions: **1a** (1.5 mmol), **2a** (1.0 mmol), base (1.0 mmol), catalyst (1.0 mol% or 10 mg), solvent (3.0 mL), 24 h, reflux.
[b] Yields of isolated product.
[c] Under air.
[d] **A**, **B**, **C** (benzoxazolyl iridium complex). ref 11.

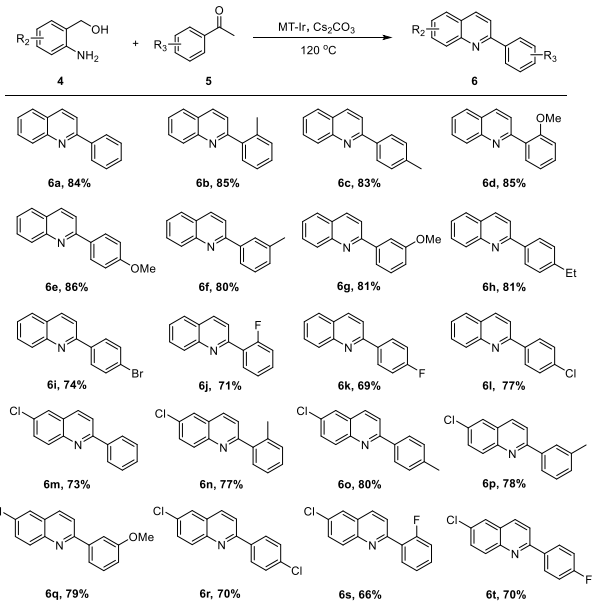
Having established the optimal reaction conditions (Table 1, entry 7), the substrate expansions were examined (Table 2). It could be found that there were relatively higher yields for the aniline with electron drawing groups in different substitution positions of the aromatic ring portion. It is very interesting to find that propan-1,3-diol and butane-1,4-diol which were fatty alcohols were all separated smoothly with moderate to good yields (**3k**-**3r**).

Table 2. Substrate expansion[a,b]



[a] Conditions: **1** (1.5 mmol), **2** (1.0 mmol), Cs_2CO_3 (1.0 mmol), MT-Ir (10 mg), toluene (3.0 mL), 110 °C, N_2, 24 h.
[b] Isolated yields based on **1**.

Table 3. Substrate expansion of quinolines synthesis[a,b]



[a] Conditions: **4** (1.0 mmol), **5** (1.2 mmol), Cs_2CO_3 (1.0 mmol), MT-Ir (10 mg), toluene (3.0 mL), 10 h, 120 °C.
[b] Isolated yields based on **5**.

To better elaborate this catalyst, quinolines synthesis was explored in the presence of MT-Ir catalyst under N_2 conditions. Interestingly, all the 2-aminobenzylalcohol was

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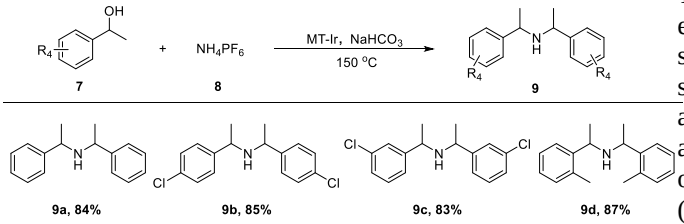
converted to the corresponding quinolines with moderate to good yields (Table 3). It was obvious to find that there were relatively high yields for the acetophenone with either electron withdrawing groups or electron donating groups which in different substitution positions of the aromatic ring portion (**6a**~**6l**). Interestingly, when the benzene ring of 2-aminobenzylalcohol was charged to the electron-withdrawing group, the yield was slightly reduced. (**6m**~**6t**).

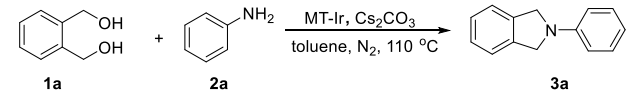
Furthermore, the alkylation reaction of ammonia salt with alcohols were carried out, since borrowing hydrogen reaction of ammonia salt is a challenging and interesting topic in organic synthesis area. All the alcohols were converted into the corresponding secondary amines with moderate to good yields in the presence of MT-Ir catalyst under N_2 conditions (Table 4). This reaction provided an effective method for the synthesis of substituted secondary amines.

Table 4. Alkylation of ammonia salt with secondary alcohols [a,b]



[a] Conditions: **7** (2.0 mL), **8** (1.0 mmol), $NaHCO_3$ (30 mmol%), MT-Ir (10 mg), 24 h, xylene, 150 °C.
[b] Isolated yields based on **8**.

The catalyst MT-Ir was centrifuged and washed with toluene. When the recovered MT-Ir was reused to catalyze the synthesis of isoindoline, it was observed that almost the same yield was achieved. The reaction could take place with slightly low yields even the recovered MT-Ir was reused for five times (Scheme 3).



Recycled times	0	1	2	3	4	5
Yields	84%	82%	79%	76%	74%	70%

Scheme 3. Recycled experiments.

To better understand the synthetic catalyst, the recovered MT-Ir was examined through X-ray power diffraction (XRD) measurement. It was found that MT-Ir still maintained good catalytic activity by comparing the results of first cycle with fifth cycle. A slight decrease in peak height indicated a loss of iridium after five cycles, which was probably the reason for the decrease in yield (Fig. 6).

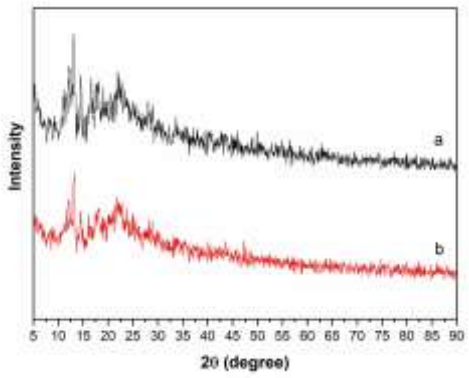
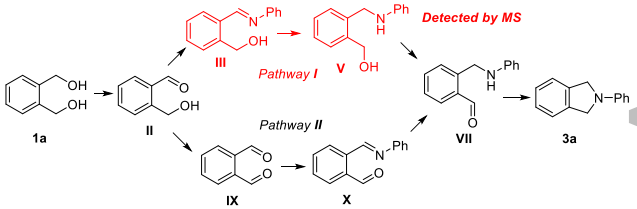


Fig. 6. XRD pattern of MT-Ir after one cycles (a) and MT-Ir after five cycles (b).

2.4. Mechanism Exploration.

With all the results in hand, we found that catalyst A, B, C or iridium chloride couldn't catalyze the synthesis of 2-arylisoindolines, while this new MT-Ir could produce high yield of desired product (Table 1, entries 7, 10-13). This is further explained and supported that triazole is an especial ligand developed by Shi and Wang during the past several years.[15] Another possible reason might be iridium sites grafted on siliceous supports, which might be able to act as multifunctional catalytic centers, activating alcohol and promoting hydrogen transfer, similar results was also observed by Fraile.[16] Furthermore, energy dispersive X-ray (EDX) images of the catalyst MT-Ir showed that more than five kind of iridium sites were examined (Fig. 2).

To better understand this catalytic system and transfromation, the preliminary mechanism exploration was carried on. One key point for this transformation is the gerenation of iridium hydride intermediate. To verify this hypothesis, the direct capture of iridium hydride intermediate was performed. MT-Ir was treated with cesium carbonate and then dealted with 1,2-phenylenedimethanol. The solid-state infrared spectra of MT-Ir revealed absorptions at 1955 cm^{-1}which is assigned to iridium-hydride stretches since it is consistent with the known chemical shift.[17]



Scheme 4. Two possible reaction pathways.

Another key point for this transformation is reaction pathway. There are two possible pathways for isoindoline synthesis (Scheme 4). According to the experiments, pathway I was considered to be possible, because the intermediate V was detected by mass spectrum (See supporting information for details), while intermediate IX and X were not found in this reaction. Importantly, the

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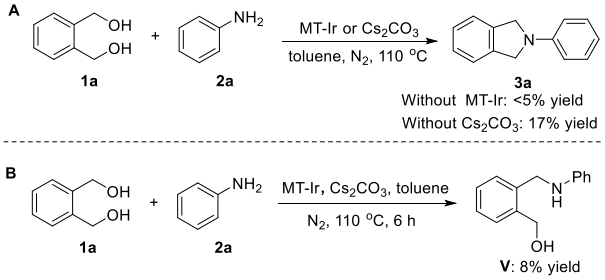
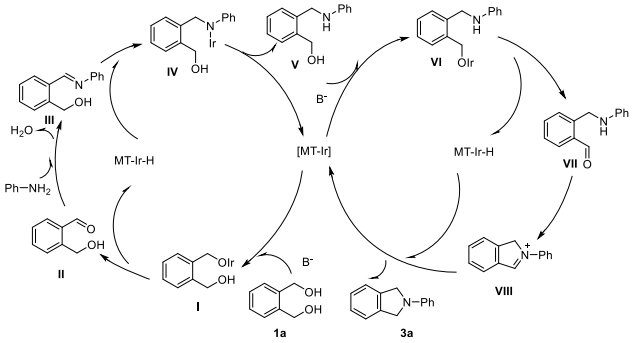
intermediate V could be separated and confirmed, despite that only very low yield was achieved (Scheme 5). Control experiments revealed that this reaction is not able to take place in the absence of MT-Ir catalyst.



Scheme 5. Control experiments and the capture of intermediate **V**.

Based on all the aforementioned mechanism exploration, a possible reaction pathway for isoindoline synthesis was proposed (Scheme 6). Initially, the hydrido-iridium species should be produced by the reaction of one hydroxyl group of 1,2-phenylenedimethanol to MT-Ir. Next, iridium hydride intermediate would be generated from β-hydrogen elimination of alkoxo moiety with the formation of the 2-(hydroxymethyl)benzaldehyde. The condensation reaction of 2-(hydroxymethyl)benzaldehyde with aniline was occurred and produced the intermediate (*E*)-(2-((phenylimino)methyl)phenyl)methanol, which was reduced using the borrowed hydrogen from iridium hydride intermediate. After the second above process, the isoindoline product was formed to complete the catalytic cycle and generate the catalyst.



Scheme 6. The proposed reaction mechanism for the synthesis of isoindolines.

Conclusions

In conclusion, we have synthesized a novel 1,2,4-triazole iridium complex and successfully achieved its covalent attachment to mesoporous MCM-41 to generate heterogeneous catalyst. The resulting catalyst has shown high efficiency in the synthesis of 2-arylisoindoline derivatives, quinolines and symmetrical secondary amines. Mechanistic experiments revealed that the reaction is initiated by alcohol dehydrogenation and promoted by iridium hydride intermediate. Importantly, the direct detection of a diagnostic iridium hydride signal confirmed that the synthesis of 2-arylisoindoline derivatives is undergoing borrowing hydrogen process.

Acknowledgments

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Keywords: triazole. iridium. isoindolines. borrowing hydrogen. mechanism

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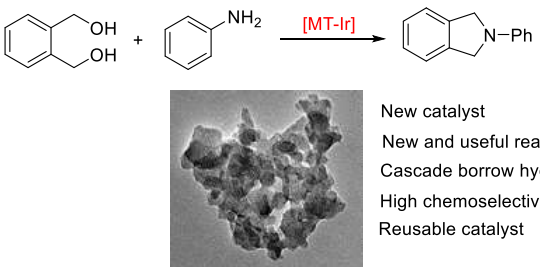

New catalyst
New and useful reaction
Cascade borrow hydrogen
High chemoselectivity
Reusable catalyst

Synthesis of 2-Arylisoindoline Derivatives Catalyzed by Reusable 1,2,4-Triazole Iridium on Mesoporous Silica through Cascade Borrowing Hydrogen Strategy

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