Catalysis Science & Technology

Accepted Manuscript

Volume 1 | Number 1 | Jan 2013 | Pages 1–100

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Cite this: DOI: 10.1039/c0xx00000x

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PAPER

Heterogeneously Biomimetic Aerobic Synthesis of 3-Iodoimidazo[1,2-*a*]pyridines via CuO_x/OMS-2-catalyzed Tandem Cyclization/iodination and Their Late-stage Functionalization

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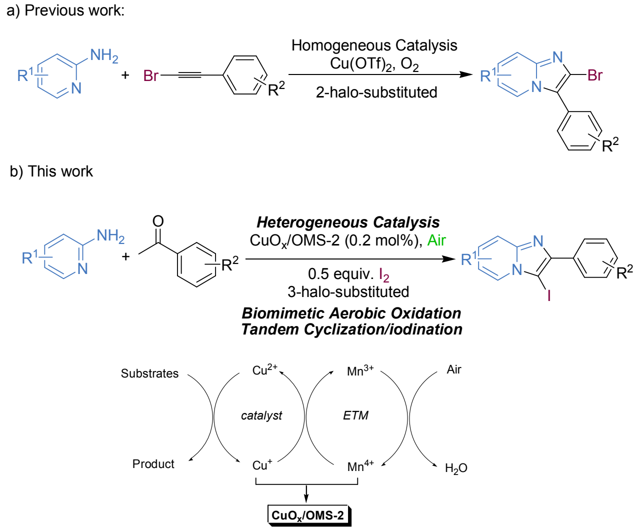
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

In the presence of supported copper on manganese-oxide-based octahedral molecular sieves OMS-2 (CuO_x/OMS-2), heterogeneously aerobic catalytic synthesis of 3-iodoimidazo[1,2-*a*]pyridines from acetophenones, 2-aminopyridines and I_2 via tandem cyclization/iodination in one-pot manner is achieved. For heterogeneous catalyst, OMS-2 acts not only as a support for catalytic Cu species but also an electron-transfer mediator (ETM) which combines with Cu to generate a low-energy pathway for rapid electron transfer. In this way, the biomimetic catalytic oxidation could directly employ air as green terminal oxidant under mild conditions and provide corresponding products with broad substrates in moderate to excellent yields using very low catalyst loading (0.2 mol% Cu). In this process, I_2 not only plays a role of catalyst for the initial cyclization with assistance of CuO_x/OMS-2, but also acts as reactant for the next electrophilic oxidative iodination, which makes the reaction highly atom economic. Besides, the late-stage functionalization of the I-substituted imidazo[1,2-*a*]pyridines is also demonstrated by various coupling, which shows its potential application in synthetic and pharmaceutical chemistry. Moreover, the catalyst is truly heterogeneous and reusable.

Introduction

As the increase of molecular complexity, one-pot multi-step reactions gradually become superior and attractive because they reduce the number of workups and purifications. Therefore, employing one-pot tandem reactions can avoid stop-and-go synthesis and subsequent cost for waste disposal, which means it is beneficial to economy and environment.[1] Furthermore, it is more meaningful and profitable to apply one-pot tandem oxidations into heterogeneous catalysis using air as green oxidant since heterogeneous catalysis has practical advantages in catalyst handling, recyclability and separation of catalyst from products.[2-4] Consequently, the development of heterogeneously aerobic one-pot tandem catalytic oxidations is highly desirable.

Imidazo[1,2-*a*]pyridines are significant pharmacophore and wildly found in many biologically active compounds. They have antibacterial,[5] antiviral,[6] antitumor[7] and anti-inflammatory[8] properties, thus they are present in best-selling drugs, such as zolpidem, alpidem, necopidem, saripidem and zolimidine.[9] A variety of synthetic methodologies have been developed,[10] focusing on (1) condensation between 2-aminopyridines and precursors like a-haloketones;[11] (2) Ag-mediated cyclization of 2-aminopyridnes and alkynes;[12] (3) Fe-catalyzed cyclization of 2-aminopyridnes and nitroolefins[13] and (4) recently Cu-catalyzed cyclization of 2-aminopyridines and ketones with assistance of I-.[14] In terms of heterogeneous catalysis, we have reported a solid-supported $CuCl_2$/nano-TiO_2-catalyzed oxidative cyclization of ketones and 2-aminopyridines without assistance of I^- most



Scheme 1 Heterogeneous biomimetic oxidative synthesis of 3-iodoimidazo[1,2-*a*]pyridines.

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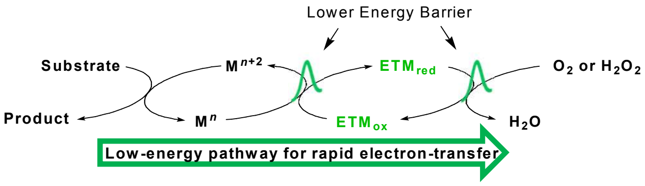
†Electronic Supplementary Information (ESI) available: [Experimental details, spectra data of the products and copies of spectra]. See DOI: 10.1039/b000000x/

recently.[15] Although exciting results have been discovered, the synthesis of halo-substituted imidazo[1,2-*a*]pyridines is rarely reported because the halide cannot be maintained on 3-position of imidazo[1,2-*a*]pyridines as long as *a*-haloketones are employed for condensation with 2-aminopyridines. Recently, Jiang`s group developed a homogeneous Cu(OTf)$_2$-catalyzed method for the synthesis of 2-halo-substituted imidazo[1,2-*a*]pyridines using 2-aminpoyridnes and haloalkynes (Scheme 1a).[16] To develop economic and environmentally benign catalytic reactions, heterogeneous catalysis for the synthesis of halo-substituted imidazo[1,2-*a*]pyridines is extremely required.

In order to use oxygen or hydrogen peroxide directly into oxidations as oxidants, Prof. Jan-E. Bäckvall and co-workers developed a biomimetic oxidative methodology that facilitating the procedures by employing electro-transfer mediators (ETMs) to decrease the redox energy barrier between catalyst and oxidant (Scheme 2).[17] Under this circumstance, ETMs generate a low-energy pathway for rapid electron transfer, which usually increases the efficiency (decreases the catalyst loading) and thus complementing the direct oxidations.[18] Based on biomimetic oxidative concept, Mizuno`s group designed a supported copper hydroxide catalyst on manganese oxide-based octahedral molecular sieve OMS-2 (Cu(OH)$_x$/OMS-2) which facilitated the oxidative homo-coupling of alkynes by generation of a rapid electron-transfer path.[19] Octahedral molecular sieve (OMS) materials of manganese oxide are crystalline, porous, mixed valent and semi-conductive; therefore they are applied into catalysis, battery materials, ion-exchange and adsorption.[20-22] We noticed that the redox potential of the MnO_2/Mn_2O_3 reaction is 1.04V which stands between potential of CuO/Cu_2O (0.75V) and O_2/H_2O (1.23V),[4a, 4e, 23] thus it is possible to prepare heterogeneous catalyst CuO$_x$/OMS-2 and perform oxidations using it to decrease redox energy barrier. In the course of investigating applications of heterogeneous catalysts in our group,[24] we proposed copper acts as substrate-selective redox catalyst while OMS-2 behaves as a combination of ETM and support, thereby forming a low-energy pathway to make electrons transfer rapidly in heterogeneous oxidative process. In the oxidative process, Cu oxidizes the substrates, then reduced Cu is reoxidized by Mn and reduced Mn is reoxidized by O_2 subsequently (Scheme 1b).



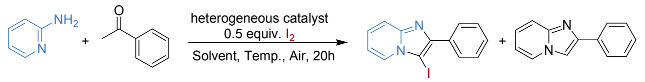
Scheme 2 Biomimetic catalytic oxidation in the presence of ETM.

Herein, we describe a heterogeneously biomimetic aerobic synthesis of 3-iodoimidazo[1,2-*a*]pyridines via CuO$_x$/OMS-2-catalyzed tandem cyclization/iodination from 2-aminopyridines, ketones and I_2 (Scheme 1b). In the oxidative procedure, OMS-2 works as support with large surface and ETM that facilitates rapid electron-transfer in the means of decreasing the energy-barrier between catalyst and oxidant, while I_2 is used as catalyst for the initial cyclization as well as dedicates itself entirely for the subsequent electrophilic oxidative iodination.

Results and discussion

The one-pot tandem oxidative synthesis of 3-iodoimidazo[1,2-*a*]pyridine from 2-aminopyridine, acetophenone and I_2 was studied using different catalysts and solvents to optimize the reaction conditions (Table 1). We anticipated the tandem reaction goes through I-catalyzed Ortoleva-King reaction[14e, 15] with assistance of copper to form imidazo[1,2-*a*]pyridine followed by copper-catalyzed iodination of it, which indicates the high yield of imidazo[1,2-*a*]pyridine is necessity of forming I-substituted product. As we expected, imidazo[1,2-*a*]pyridine **3aa** was the major product if the reaction was ran without adding metal catalyst (Table 1, entry 1). When OMS-2 was directly used as catalyst, the moderate yield of desired product **3a** was obtained although **3aa** was still isolated in 29% (Table 1, entry 2). To our delight, supported Cu(OH)$_x$/OMS-2 and CuO$_x$/OMS-2 (6mg, 0.2 mol%, Cu: 1.3 wt%, see the Experimental Section for the preparation) brought about good results and the latter one provided single desired 3-iodoimidazo[1,2-*a*]pyridine in excellent yield (Table 1, entries 3 and 4). Subsequently, unsupported CuO was found not efficient for this tandem reaction, even though the longer reaction time was employed (Table 1, entry 5). In addition, a physical mixture of bulk CuO (1 mol%) and OMS-2 (6mg) did not selectively give **3a** in high yield (Table 1, entry 6). These results demonstrated that highly dispersed copper species on OMS-2 could play a key role during tandem reaction. So

Table 1 Optimization of the reaction conditions[a]



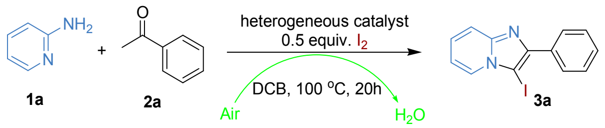
1a **2a** **3a** **3aa**

Entry	Catalyst	Solvent	Temp. (ºC)	Yield[b] (%)	
				3a	**3aa**
1		DCB	100	10	89
2	OMS-2	DCB	100	50	29
3	Cu(OH)$_x$/OMS-2	DCB	100	81	0
4	**CuO$_x$/OMS-2**	**DCB**	**100**	**93**	**0**
5	CuO	DCB	100	8 (14[c])	75 (60[c])
6	CuO + OMS-2	DCB	100	52	30
7	CuO$_x$/OMS-2	DCB	r.t.	0	39
8	CuO$_x$/OMS-2	DCB	50	0	45
9	CuO$_x$/OMS-2	DCB	80	0	63
10	CuO$_x$/OMS-2	DCB	150	89	0
11	CuO$_x$/OMS-2	DMSO	100	0	0
12	CuO$_x$/OMS-2	DMF	100	0	20
13	CuO$_x$/OMS-2	*o*-xylene	100	0	32
14	CuO$_x$/OMS-2	1,4-dioxane	100	0	45
15[d]	CuO$_x$/OMS-2	DCB	100	48	0
16[e]	CuO$_x$/OMS-2	DCB	100	72	0
17[f]	CuO$_x$/OMS-2	DCB	100	90	0
18[g]	CuO$_x$/OMS-2	DCB	100	0	78
19[h]	CuO$_x$/OMS-2	DCB	100	92	0
20[i]	CuO$_x$/OMS-2	DCB	100	85	0
21[j]	CuO$_x$/OMS-2	DCB	100	0	0

[a] Reaction Conditions: 2-aminopyridine (0.6 mmol), acetophenone (0.5 mmol), I_2 (0. 25 mmol), catalyst (6 mg), solvent (1 mL), air, 20h. [b] Isolated yields. [c] For 48h. [d] 6 mg of CuO$_x$/OMS-2 (Cu: 0.3 wt%) was used. [e] 3 mg of CuO$_x$/ OMS-2 was used. [f] 12 mg of CuO$_x$/OMS-2 was used. [g] Under N_2 atmosphere. [h] Under O_2 atmosphere. [i] For 48h. [j] In the absence of I_2.

CuO_x/OMS-2 was chosen to optimize the reaction temperature. It was found that the temperature below 100 °C could not offer desired product at all and the reaction stopped at the initial cyclization rather than finishing the next iodination (Table 1, entries 7-9). However, higher temperature (150 °C) did not result in higher yield, which means the heterogeneous catalyst can make reaction carry out at mild temperature (Table 1, entry 10). Then, various solvents were studied in the reactions and only polar DCB (*o*-dichlorobenzene) could provide desired product while other examined solvents just offered cyclized product to some extent (Table 1, entries 11-14). Notably, the DMSO led to 2-aryl-3-(pyridine-2-ylamino)imidazo[1,2-*a*]pyridine as the single product instead of **3a** and **3aa** (Table 1, entry 11), which was the same as the discovery by Wu`s group.[25] For amounts of catalyst, the inferior results were found if the loading of CuO_x/OMS-2 or the amount of Cu supported on OMS-2 were decreased (Table1, entries 15 and 16). On the other hand, increased loading of heterogeneous catalyst could not better the yield as well (Table 1, entry 17). Subsequently, it was found that atmosphere of the reaction affected the tandem reaction seriously (Table 1, entries 18 and 19). N_2 suppressed the iodination of tandem reaction definitely while O_2 was favorable to it, which means the reaction ended at the first stage (cyclization) without oxidant and the iodination of tandem reaction is aerobic. Thus, air was chosen to be the efficient green oxidant for this tandem reaction. Moreover, the extended reaction time did not increase the yield of iodo-substituted product as well (Table 1, entry 20). Finally, the controlled experiment under iodine-free condition did not give any products at all, which conformed the tandem reaction mechanically undergoes initial I-catalyzed Ortoleva-King reaction with assistance of copper (Table 1, entry 21).

Table 2 Optimization of heterogeneous catalyst[a]



Entry	Catalyst	Isolated Yield (%)
1	**CuO_x/OMS-2**	**93**
2	CuO_x-MnO_x/Al-Ti	25
3	CuO_x-FeO_x/OMS-2	59
4	CuO_x-FeO_x/C	18
5	CuO_x/Al-Ti	27
6	CuO_x/nano-TiO_2	44
7	CuO_x/C	24
8	CuO_x/ATP	15

[a] Reaction Conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), I_2 (0.25 mmol), heterogeneous catalyst (6 mg), DCB (1 mL), 100 °C, air, 20h.

Next, more tests of heterogeneous catalysts were carried out for further optimizing the reaction condition (Table 2). Firstly, many bimetallic catalysts loaded on various supports were applied into the tandem reaction. CuO_x-MnO_x/Al-Ti did not lead to an improvement in overall efficiency although Cu and Mn were supposed to generate a low-energy path as what CuO_x/OMS-2 does (Table 2, entries 1 and 2). In addition, other bimetallic catalysts, like CuO_x-FeO_x/OMS-2 and CuO_x-FeO_x/C, did not improve the tandem reaction as well (Table 2, entries 3 and 4). Lastly, the reactions were performed using copper oxide supported on different supports as heterogeneous catalysts (Table 2, entries 5-8). Consequently, Al-Ti, nano-TiO_2, charcoal and ATP (attapulgite) did not show better results than OMS-2 though CuO_x/nano-TiO_2 brought about desired product in moderate yield. Therefore, it was proven that OMS-2 is the most suited support for the reaction (Table 2, entries 1 and 5-8).

After confirming the superiority of CuO_x/OMS-2 in this tandem reaction, the heterogeneous catalyst was characterized by TEM, XRD and XPS. Specifically, the TEM image of the catalyst showed OMS-2 was composed of short nanorods which were structurally single crystanlline[21] and dispersed granular CuO was attached on OMS-2 (Figure 1, left). The X-ray diffraction (XRD) pattern of CuO_x/OMS-2 was the same as that of the parent OMS-2 support and no signals due to copper metal (cluster) or copper oxide were observed (Figure 1, right), which further suggested copper oxide is highly dispersed on OMS-2. The X-ray photoelectron spectroscopy (XPS) profile showed the banding energies of Cu $2p_{3/2}$ at 933.8 eV and Cu $2p_{1/2}$ at 954.3 eV respectively (Figure 2, left), and the shake-up satellite peaks at around 940-944 eV, which suggests the oxidation state of copper species is +2.[19, 26] Besides, the XPS profile of Mn 2p was also demonstrated in Figure 2 (right).[19]

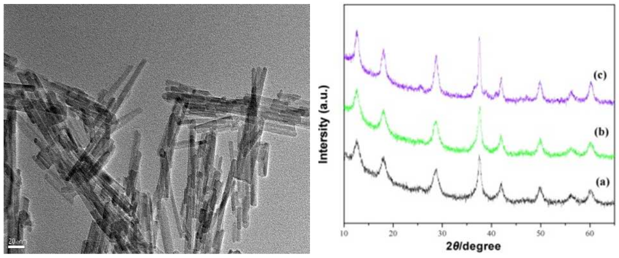


Figure 1 TEM image of CuO_x/OMS-2 (left); XRD patterns (right) of (a) OMS-2, (b) CuO_x/OMS-2 and (c) CuO_x/OMS-2 after the first use.

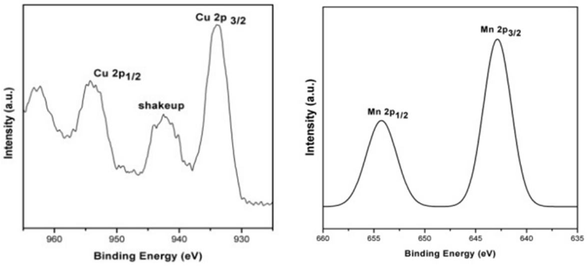
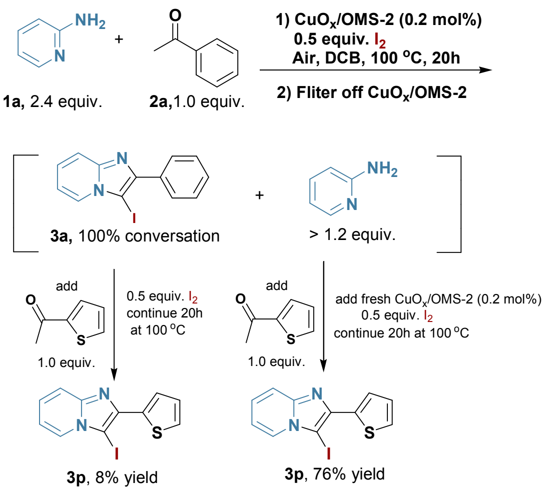


Figure 2 XPS profiles of Cu 2p (left) and Mn 2p (right).

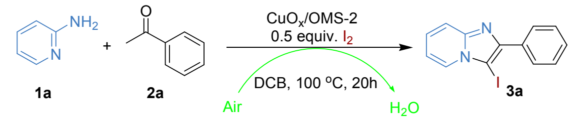
To verify whether the obvious catalysis is derived from solid CuO_x/OMS-2 or the leached copper species, the tandem reaction of **1a**, **2a** and I_2 was run, and then catalyst was removed after filtering a totally converted reaction mixture. Next, another ketone (1.0 equiv. 2-acetylthiophene) and 0.5 equiv. I_2 were added into the filtrate together, and then the filtrate was treated with the rest of 2-aminopyridine (>1.2 equiv.) under the standard conditions. Consequently, only 8% of **3p** was isolated, while 76% yield of **3p** was obtained if fresh CuO_x/OMS-2 and 0.5 equiv. I_2 were put into the filtrate (Scheme 3). ICP-AES was applied into analysis of the filtrate that was removed by CuO_x/OMS-2, which confirmed no copper species was detected in the filtrate (Cu: below 0.001%). Above results indicated that the catalysis is from the solid catalyst instead of the leached copper species and the catalyst is unambiguously heterogeneous in nature.



Scheme 3 The Test of Heterogeneous System

After completion of the tandem reaction catalyzed by CuO$_x$/OMS-2, the catalyst was easily isolated from the reaction mixture by filtration. The XRD demonstrated the structure of reused catalyst was preserved (Figure 1, right) and the retrieved catalyst showed the high catalytic ability for the second run. Finally, it was found that the catalyst could be reused three times with a slight decrease in catalytic ability and the catalytic ability can be regenerated by calcination at 350 °C for 2h under air atmosphere (Table 3).

Table 3 Recycling of CuO$_x$/OMS-2^a

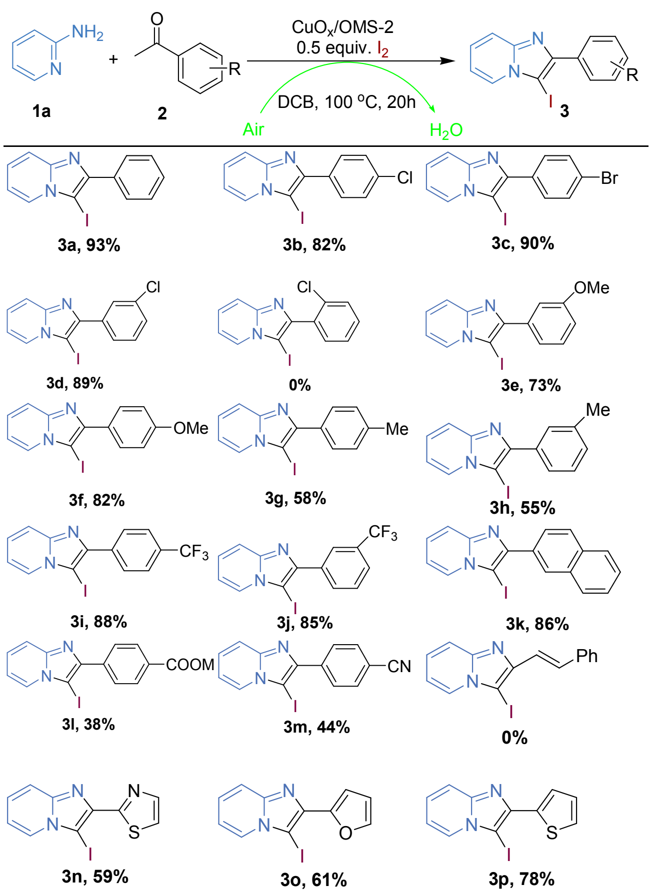


Cycle	1	2	3	4	5^b
Isolated yield of **3a** (%)	93	89	81	69	90

^{a} Reaction conditions: 2-aminopyridine (0.6 mmol), acetophenone (0.5 mmol), I$_2$ (0.25 mmol), CuO$_x$/OMS-2 (6 mg, 0.2 mol%), DCB (1 mL), air, 100°C, 20h. ^{b} Regenerated catalyst was used.

The substrate scope of the reactions was examined using 0.2 mol% CuO$_x$/OMS-2 as efficient catalyst. Initially, 2-minopyridine **1a** and various substituted acetophenones **2** were used as substrates to expand the reaction scope under optimized reaction conditions (Table 4). Generally, substituted acetophenones with electro-donating and electro-withdrawing groups could participate in the tandem reactions efficiently, except ortho-substituted ones, like 2-Cl-acetophenone, did not give any desired products because of steric hindrance. Specifically, electro-deficient acetophenones, including halogen and CF$_3$, provided higher yields of desired products than electro-rich ones did, such as methyl, methoxyl, COOMe and cyano, probably because the iodination of tandem reaction is electrophilic aromatic substitution (Table 4, **3a-3m**). Furthermore, ketones containing heteroatoms reacted with 2-aminopyridine and I$_2$ efficiently and the moderate to good yields 59-78% were obtained (Table 4, **3n-3p**). However, *α,β*-unsaturated ketone, such as benzalacetone, did not offer any desired product at all perhaps because the *α,β*-unsaturated double bond affected the iodination.

Table 4 The scope of the tandem reaction using 2-aminopyridne, I$_2$ and ketones^a



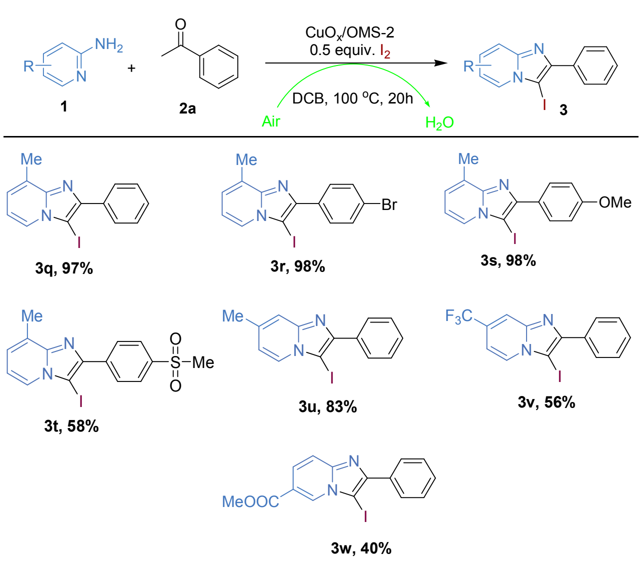
^{a} Reaction Conditions: **1a** (0.6 mmol), **2** (0.5 mmol), I$_2$ (0.25 mmol) CuO$_x$/OMS-2 (0.2 mol%, 6 mg), DCB (1.0 mL), air, 100 °C, 20h, isolated yields.

Next, more scope examinations were performed using different substituted 2-aminopyridines and many acetophenones as raw materials (Table 5). When 3-metyl-2-aminopyridne was used as substrate to react with electro-poor and electro-rich acetophenones, almost quantitative yields of products were obtained (Table 5, **3q-3s**). However, methylsufonyl substituted acetophenone only provided moderate yield of I-sustituted imidazo[1,2-*a*]pyridine (Table 5, **3t**). Then, it was found that other substituted 2-aminopyridines, like Me-, CF$_3$- and COOMe-, were also tolerated in this tandem reaction and gave moderate to good yields of desired products (Table 5, **3u-3w**).

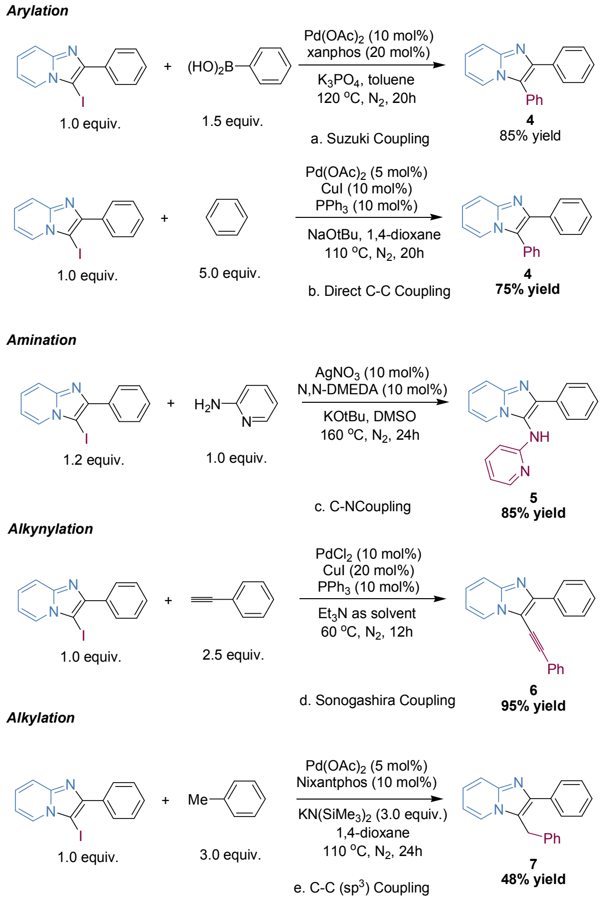
As we known, I-substituted aromatic heterocycles are versatile reaction partners for many kinds of coupling reactions since the iodine is an excellent leaving group.[27] Here, we report several applications of 3-iodoimidazo[1,2-*a*]pyridine as a versatile building block for further functionalization via coupling technics (Scheme 4, synthetic methods see Supporting Information).

Firstly, Suzuki reaction was studied by using **3a** and phenylboronic acid as coupling reagents under basic Pd-catalyzed reaction condition, and the corresponding product **4** was isolated in 85% (Scheme 4a).[16, 28] More importantly, the direct arylation of 3-iodoimidazo[1,2-*a*]pyridine using excessive amount of benzene as the arylating reagent under Pd/Cu-cocatalysis was also achieved although the yield of arylated product **4** was slightly low (Scheme 4b).[29] Subsequently, Ullmann-type C-N bond-formation was performed successfully using 2-aminopyridine as aminating reagent under a Ag-mediated condition at relatively high temperature (Scheme 4c).[30] Next, an excellent yield of 2-phenyl-3-(2-phenylethynyl)H-imidazo[1,2-*a*]pyridine **6** was observed when Sonogashira coupling was conducted under a standard Sonogashira condition (Scheme 4d).[31] Lastly, a challengeable C(sp^2)-C(sp^3) bond-formation was realized by using toluene as reaction partner under Pd-catalyzed condition (Scheme 4e). Surprisingly, the desired alkylated product **7** was observed under assistance of ligand Nixantphos and excessive KN(SiMe$_3$)$_2$ even though the yield was not high.[32]

Table 5 The scope of the tandem reaction using substituted 2-aminopyridines, I$_2$ and acetophenone [a]

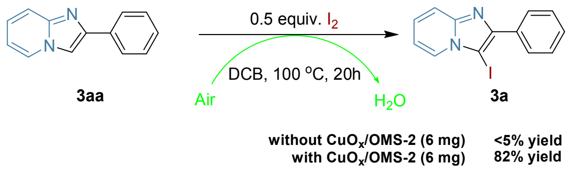


[a] Reaction Conditions: **1** (0.6 mmol), **2a** (0.5 mmol), I$_2$ (0.25 mmol), CuO$_x$/OMS-2 (6 mg, 0.2 mol%), DCB (1 mL), air, 100°C, 20h, isolated yields.



Scheme 4 Late-stage functionalizations of 3-iodoimidazo[1,2-*a*]pyridine via various couplings.

For understanding the mechanism of this tandem reaction, control experiments were run. If imidazo[1,2-*a*]pyridine **3aa** was directly used as raw material with I$_2$ in DCB at 100 °C for 20h under air , almost no **3a** was isolated without adding CuO$_x$/OMS-2. Reversely, 82% yield of **3a** was obtained if 6mg CuO$_x$/OMS-2 was added into the reaction (Scheme 5). Additionally, CuO$_x$/OMS-2 cannot catalyze the synthesis of imidazo[1,2-*a*]pyridine **3aa** between 2-aminopyridine and acetophenone without I$_2$ under oxidative condition at certain temperature.[15] Therefore, the tandem reaction makes up of an I-catalyzed Ortoleva-King reaction with assistance of Cu and a subsequent CuO$_x$/OMS-2-catalyzed electrophilic oxidative iodination. Initially, *α*-iodination of acetophenone was realized catalyzed by CuO$_x$/OMS-2 using I$_2$ as an iodinating reagent under air.[33] Next, imidazo[1,2-*a*]pyridine was generated between *α*-iodo acetophenone and 2-aminopyridine via Ortoleva-King reaction followed by cyclization and I$_2$ was regenerated by oxidation of oxygen to finish the initial cyclization cycle.[11g, 14e, 15] Then, oxidative iodination of electro-rich imidazo[1,2-*a*]pyridine was performed on the most acidic C-H bond via CuO$_x$/OMS-2-catalyzed electrophilic aromatic substitution.[27a, 34] Eventually, reduced copper species (I) was reoxidized by Mn(IV) to turn back to copper species (II) and reduced Mn was reoxidzed by O$_2$ in air via a biomimetic oxidation pathway (Scheme 1b).[19]



Scheme 5 Control Experiments

Conclusions

In summary, an efficient biomimetic aerobic oxidative tandem cyclization/iodination for the synthesis of 3-iodoimidazo[1,2-*a*]pyridines from 2-aminopydines, acetophenones and I$_2$ catalyzed by heterogeneous CuO$_x$/OMS-2 was successfully developed. This tandem reaction underwent a cyclization dominated by an I-catalyzed Ortoleva-King reaction and copper-catalyzed electrophilic oxidative iodination, which brought about 100% iodine atom economy. The tandem reactions tolerated a large range of substrates and gave moderate to great yields of products that could be applied into versatile late-stage functionalizations. Specially, CuO_x/OMS-2 generated a low-energy pathway for the rapid electron transfer during the oxidative process because OMS-2 plays a multiple role of support and electron-transfer mediator (ETM), which enabled air to be direct oxidant smoothly. Furthermore, the well-dispersed low-loading heterogeneous catalyst can be reused three times without significant loss of catalytic ability.

Experimental

General

All reagents were purchased from commercial suppliers and used without further purification. Metal salts and catalyst supports were commercially available and were used directly. All experiments were carried out under air. Flash chromatography was carried out with Merck silica gel 60 (200-300 mesh). Analytical TLC was performed with Merck silica gel 60 F254 plates, and the products were visualized by UV detection. ^1H NMR and ^{13}C NMR (400 and 100 MHz respectively) spectra were recorded in $CDCl_3$. Chemical shifts (δ) are reported in ppm using TMS as internal standard, and spin-spin coupling constants (J) are given in Hz. All heterogeneous catalysts are synthesized by wet impregnation in deionized water and $Cu(OH)_x$/OMS-2 is made by deposition-precipitation in water.

Preparation of OMS-2[20a]

5.89g of $KMnO_4$ in 100 mL of deionized water was added to a solution of 8.8g of $MnSO_4$-H_2O in 30 mL of deionized water and 3 mL concentrated HNO_3. The solution was refluxed at 100 °C for 24 h, and the product was filtered, washed, and dried at 120 °C for 8 hours. Finally, the dry OMS-2 was calcined in a muffle furnace at 350 °C for 2 hours. Then, the black powder OMS-2 was obtained.

Preparation of CuO_x/OMS-2[20a]

Support OMS-2 (2g) was added to a 50 mL round-bottom flask. A solution of $Cu(NO_3)_2\cdot 3H_2O$ (0.15g) in deionized water (10 mL) was added to OMS-2, and additional deionized water (10 mL) was added to wash down the sides of the flask. Then the flask was submerged into an ultrasound bath for 3h at room temperature and stirred for further 20h at room temperature. After that, the water was distilled under reduced pressure on a rotary evaporator at 80 °C for more than 2h. Finally, the black powder was dried into an oven at 110 °C for 4 hours followed by calcination at 350 °C for 2 hours. The Inductive Coupled Plasma Optical Emission Spectrum (ICP-OES) showed Cu content is 1.31 wt%.

General procedure for CuO_x/OMS-2-catalyzed tandem reaction

CuO_x/OMS-2 (6 mg, 0.2 mol%), 2-aminopyridine (0.6 mmol), acetophenone (0.5 mmol), I_2 (0.25 mmol) and DCB (1 mL) were added to a flask with a bar. The flask was stirred at 100 °C for 20h under air. After cooling to room temperature, the mixture was diluted with ethyl acetate and filtered. The filtrate was removed under reduced pressure to get the crude product, which was further purified by silica gel chromatography (petroleum/ethyl acetate = 4/1 as eluent) to yield corresponding product. The identity and purity of the products was confirmed by ^1H and ^{13}C NMR spectroscopic analysis and HRMS.

Notes and References

1 (*a*) M. J. Climent, A. Corma and S. Iborra, *Chem. Rev.,* 2011, **111**, 1072; (*b*) M. J. Climent, A. Corma and S. Iborra, *RSC Adv*., 2012, **2**, 16.

2 M. J. Climent, A. Corma, S. Iborra and M. J. Sabater, *ACS Catal*., 2014, **4**, 870.

3 Selective reviews on heterogeneous catalysis, see: (*a*) M. Sankar, N. Dimitratos, P. J. Miedziak, P. P. Wells, C. J. Kiely and G. J. Hutchings, *Chem. Soc. Rev.*, 2012, **41**, 8099; (*b*) N. Mizuno and M. Misono, *Chem. Rev.*, 1998, **98**, 199; (*c*) E.-J. Ras and G. Rothenberg, *RSC Adv.*, 2014, **4**, 5963; (*d*) J. M. Campelo, D. Luna, R. Luque, J. M. Marinas and A. A. Romero, *ChemSusChem,* 2009, **2**, 18; (*e*) R. A. Sheldon and H. V. Bekkum, Fine Chemicals through Heterogeneous Catalysis, Wiley-VCH: Weinheim, 2001.

4 For the selected papers on the application of solid-supported heterogeneous catalysts, see: (*a*) X. Meng, X. Xu, T. Gao and B. Chen, Eur. *J. Org. Chem*., 2010, 5409; (*b*) R. N. B. Baig and R. S. Varma, *Green Chem.,* 2013, **15**, 1838; (*c*) D. D. Tang, K. D. Collins and F. Glorius, *J. Am. Chem. Soc.,* 2013, **135**, 7450; (*d*) C. Liu, X. Rao, Y. Zhang, X. Li, J. Qiu and Z. Jin, *Eur. J. Org. Chem*., 2013, 4345; (*e*) X. Meng, C. Yu and P. Zhao, *RSC Adv.,* 2014, **4**, 8612; (*f*) J. B. Bharate, S. K. Guru, S. K. Jain, S. Meena, P. P. Singh, S. Bhushan, B. Singh, S. B. Bharate and R. A. Vishwakarma, *RSC Adv.,* 2013, **3**, 20869.

5 (*a*) M. H. Fisher and A. Lusi, *J. Med. Chem.,* 1972, **15**, 982; (*b*) J. C. Teulade, G. Grassy, J. P. Girard and J. P. Chapat, *Eur. J. Med. Chem*., 1978, **13**, 271.

6 (*a*) A. Gueiffier, M. Lhassani, A. Elhakmaoui, R. Snoeck, G. Andrei, O. Chaxignon, J. C. Teulade, A. Kerbal, E. M. Essassi, J. C. Debouzy, M. Witvrouw, Y. Blache, J. Balzarini, E. De Clercq and J. P. Chapat, *J. Med. Chem.,* 1996, **39**, 2856; (*b*) M. Lhassani, O. Chavignon, J. M. Chezal, J. C. Teulade, J. P. Chapat, R. Snoeck, G. Andrei, J. Balzarini, E. De Clercq and A. Gueiffier, *Eur. J. Med. Chem.,* 1999, **34**, 271.

7 (*a*) E. Badaway, T. Kappe, *Eur. J. Med. Chem*., 1995, **30**, 327; (*b*) M. Hranjec, I. Piantanida, M. Kralj, L. Suman, K. Pavelıć and G. Karminski-Zamola, *J. Med. Chem*., 2008, **51**, 4899; (*c*) M. Hranjec, M. Kralj, I. Piantanida, M. Sedıć, L. Suman, K. Pavelıć and G. Karminski-Zamola, *J. Med. Chem.,* 2007, **50**, 5696.

8 C. Hamdouchi, J. De Blas, M. del Prado, J. Gruber, B. A. Heinz and L. Vance, *J. Med. Chem*., 1999, **42**, 50.

9 (*a*) M. Baumann, I. R. Baxendale, S. V. Ley and N. Nikbin, *Beilstein J. Org. Chem.,* 2011, **7**, 442; (*b*) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba and W. Murmann, *J. Med. Chem*., 1965, **8**, 305; (*c*) S. Z. Langer, Z. Arbilla, J. Benavides and B. Scatton, *Adv. Biochem. Psychopharmacol*., 1990, **46**, 61; (*d*) K. Mizushige, T. Ueda, K. Yukiiri and H. C. Suzuki, *Drugs Rev*., 2002, **20**, 163; (*e*) R. J. Boerner and H. J. Moller, *Psychopharmakotherapie,* 1997, **4**, 145.

10 Selective recent papers on homogeneous synthesis of imidazopyridines using non-ketones/2-aminopyridine substrates, see: (*a*) E. P. A. Talbot, M. Richardson, J. M. McKenna and F. D. Toste, *Adv. Synth. Catal.,* 2014, **356**, 687; (*b*) H. Huang, X. Ji, X. Tang, M. Zhang, X. Li and H. Jiang, *Org. Lett.,* 2013, **15**, 6254; (*c*) J. Yu, Y. Jin, H. Zhang, X. Yang and H. Fu, *Chem. Eur. J.,* 2013, **19**, 16804; (*d*) K. B. Puttaraju and K. Shivashankar, *RSC Adv.,* 2013, **3**, 20883; (*e*) N. Chernyak and V. Gevorgyan, *Angew. Chem*., 2010, **122**, 2803; *Angew. Chem. Int. Ed*., 2010, **49**, 2743; (*f*) I. R. Siddiqui, P. Rai, Rahila, A. Srivastava and S. Shamim, *Tetrahedron Lett.,* 2014, **55**, 1159.

11 (*a*) E. S. Hand and W. W. Paudler, *J. Org. Chem*., 1978, **43**, 2900; (*b*) N. Denora, V. Laquintana, M. G. Pisu, R. Dore, L. Murru, A. Latrofa, G. Trapani and E. Sanna, *J. Med. Chem.,* 2008, **51**, 6876; (*c*) D. Zhu, J. Chen, D. Wu, M. Liu, J. Ding and H Wu, *J. Chem. Res*., 2009, **2**, 84; (*d*) D.-J. Zhu, J.-X. Chen, M.-C. Liu, J.-C. Ding and H.-Y. Wu, *J. Braz. Chem. Soc*., 2009, **20**, 482; (*e*) S. E. Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Tetrahedron Lett.*, 2003, **44**, 6265; (*f*) M. Ueno, T. Nabana and H. Togo, *J. Org. Chem.,* 2003, **68**, 6424; (*g*) A. J. Stasyuk, M. Banasiewicz, M. K. Cyrański and D. T. Gryko, *J. Org. Chem*., 2012, **77**, 5552; (*h*) T. J. Donohoe, M. A. Kabeshov, A. H. Rathi and I. E. D. Smith, *Org. Biomol. Chem*., 2012, **10**, 1093; (*i*) Z.-G. Le, Z.-B. Xie and J.-P. Xu, *Molecules*, 2012, **17**, 13368; (*j*) J.S. Yadav, B.V. Subba

Reddy, Y. Gopal Rao, M. Srinivas and A.V. Narsaiah, *Tetrahedron Lett.*, 2007, **43**, 7717; (*k*) Y.-Y. Xue, Z.-C. Chen and Q.-G. Zheng, *Synthesis*, 2002, **11**, 1505; (*l*) S. Kumar and D. P. Sahu, *ARKIVOC*, 2008, ***xv***. 88; (*m*) A. R. Katritzky, D. O. Tymoshenko, D. Monteux, V. Vvedensky, G. Nikonov, C. B. Cooper and M. Deshpande, *J. Org. Chem.*, 2000, **65**, 8059.

12 C. He, J. Hao, H. Xu, Y. Mo, H. Liu, J. Han and A. Lei, *Chem. Commun.*, 2012, **48**, 11073.

13 S. Santra, A. K. Bagdi, A. Majee and A. Hajra, *Adv. Synth. Catal.*, 2013, **355**, 1065.

14 (*a*) A. K. Bagdi, M. Rahman, S. Santra, A. Majee and A. Hajra, *Adv. Synth. Catal.,* 2013, **355**, 1741; (*b*) D. C. Mohan, R. R. Donthiri, S. N. Rao and S. Adimurthy, *Adv. Synth. Catal.,* 2013, **355**, 2217; (*c*) Z.-J. Cai, S.-Y. Wang and S.-J. Ji, *Adv. Synth. Catal.,* 2013, **355**, 2686; (*d*) K. Pericherla, P. Kaswan, P. Khedar, B. Khungar, K. Parang and A. Kumar, *RSC Adv.*, 2013, **3**, 18923; (*e*) Y. Zhang, Z. Chen, W. Wu, Y. Zhang and W. Su, *J. Org. Chem.*, 2013, **78**, 12494.

15 X. Meng, Y. Wang, C. Yu and P. Zhao, *RSC Adv.,* 2014, **4**, 27301.

16 Y. Gao, M. Yin, W. Wu, H. Huang and H. Jiang, *Adv. Synth. Catal.,* 2013, **355**, 2263.

17 For review on biomimetic aerobic oxidation, see: J. Piera and J. E. Bäckvall, *Angew Chem*., 2008, **120**, 3558; *Angew. Chem. Int. Ed.,* 2008, **47**, 3506.

18 Selective papers on biomimetic oxidation catalyzed by transition-metal and ETM, see: (*a*) B. P. Babu, X. Meng and J. E. Bäckvall, *Chem. Eur. J.*, 2013, **19**, 4140; (*b*) Y. Endo and J. E. Bäckvall, *Chem. Eur. J.,* 2011, **17**, 12596; (*c*) B. P. Babu, Y. Endo and J. E. Bäckvall, *Chem. Eur. J.*, 2012, **18**, 11524; (*d*) M. Johansson, B. W. Purse, O. Terasaki and J. E. Bäckvall, *Chem. Eur. J.,* 2008, **350**, 1807; (*e*) N. Gigant and J. E. Bäckvall, *Org. Lett.*, 2014, **16**, 1664; (*f*) N. Gigant and J. E. Bäckvall, *Chem. Eur. J.,* 2013, **19**, 10799; (*g*) X. Meng, C. Li, B. Han, T. Wang and B. Chen, *Tetrahedron,* 2010, **66**, 4029.

19 T. Oishi, K. Yamaguchi and N. Mizuno, *ACS Catal.,* 2011, **1**, 1351.

20 (*a*) R. N. DeGuzman, Y.-F. Shen, E. J. Neth, S. L. Suib, C.-L. O`Young, S. Levine and J. M. Newsam, *Chem. Mater*., 1994, **6**, 815; (*b*) Y. F. Shen, R. P. Zerger, R. N. DeGuzman, S. L. Suib, L. McCurdy, D. I. Potter and C. L. O'Young, *Science,* 1993, **260**, 511; (*c*) S. L. Suib, *J. Mater. Chem*., 2008, **18**, 1623; (*d*) S. L. Suib, *Acc. Chem. Res*., 2008, **41**, 479.

21 Selective recent papers on OMS-2-catalysis, see: (*a*) J. R. Kona, C. K. King`ondu, A. R. Howell and S. L. Suib, *ChemCatChem,* 2014, **6**, 749; (*b*) K. Yamaguchi, H. Kobayashi, T. Oishi and N. Mizuno, *Angew. Chem*., 2012, **124**, 559; *Angew. Chem. Int. Ed.,* 2012, **51**, 544; (*c*) K. Yamaguchi, Y. Wang and N. Mizuno, *ChemCatChem,* 2013, **5**, 2835; (*d*) K. Yamaguchi, H. Kobayashi, Y. Wang, T. Oishi, Y. Ogasawara and N. Mizuno, *Catal. Sci. Technol.,* 2013, **3**, 318; (*e*) Y. Wang, H. Kobayashi, K. Yamaguchi and N. Mizuno, *Chem. Commun.,* 2012, **48**, 2642; (*f*) L. Jin, J. Reutenauer, N. Opembe, M. Lai, D. J. Martenak, S. Han and S. L. Suib, *ChemCatChem,* 2009, **1**, 441; (*g*) S. Dharmarathna, C. K. King`ondu, W. Pedrick, L. Pahalagedara and S. L. Suib, *Chem. Mater.,* 2012, **24**, 705; (*h*) N. N. Opembe, Y. C. Son, T. Sriskandakumar and S. L. Suib, *ChemSusChem,* 2008, **1**, 182; (*i*) R. Kumar, S. Sithambaram and S. L. Suib, *J. Catal*., 2009, **262**, 304; (*j*) S. Sithambaram, L. Xu, C. H. Chen, Y. Ding, R. Kumar, C. Calvert and S. L. Suib, *Catal. Today,* 2009, **140**, 162; (*k*) X. Jin, K. Yamaguchi and N. Mizuno, *RSC Adv.*, 2014, **4**, 34712.

22 Selective papers on OMS-2 used as support for heterogeneous catalysis, see: (*a*) X. Jin, K. Yamaguchi and N. Mizuno, *Angew. Chem.,* 2014, **126**, 465; *Angew. Chem. Int. Ed.,* 2014, **53**, 455; (*b*) K. Yamaguchi, Y. Wang, T. Oishi, Y. Kuroda and N. Mizuno, *Angew. Chem*., 2013, **125**, 5737; *Angew. Chem. Int. Ed.,* 2013, **52**, 5627.

23 The data of redox potentials (in water at pH = 0) were obtained from the following reference: M. Pourbaix, *Atlas of Electrochemical Equilibria in Aqueous Solutions*; NACE: Houston, 1966.

24 (*a*) J. Liu, C. Yu, P. Zhao and G. Chen, *Applied Surface Science,* 2012, **258**, 9096; (*b*) C. Yu, P. Zhao, G. Chen and B. Hu, *Applied Surface Science,* 2011, **257**, 7727.

25 Z. Fei, Y. Zhu, M. Liu, F. Jia and A. Wu, *Tetrahedron Lett.,* 2013, **54**, 1222.

26 J.-L. Cao, G.-S. Shao, Y. Wang, Y. Liu and Z.-Y. Yuan, *Catal. Commun.,* 2008, **9**, 2555.

27 (*a*) S. Stavber, M. Jereb and M. Zupan, *Synthesis,* 2008, ***10***, 1487; (*b*) F. Monnier and M. Taillefer, *Angew. Chem*., 2009, **121**, 7088; *Angew. Chem. Int. Ed.,* 2009, **48**, 6954; (*c*) S. V. Ley and A. W. Thomas, *Angew. Chem.,* 2003, **115**, 5558; *Angew. Chem. Int. Ed.,* 2003, **42**, 5400.

28 (*a*) A. Suzuki, *Angew. Chem.,* 2011, **123**, 6854; *Angew. Chem. Int. Ed.*, 2011, **50**, 6723; (*b*) E. Negishi, *Angew. Chem.,* 2011, **123**, 6870; *Angew. Chem. Int. Ed.*, 2011, **50**, 6738.

29 D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev*., 2007, **107**, 174.

30 C. Sambiagio, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Soc. Rev*., 2014, **43**, 3525.

31 (*a*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett*., 1975, 4467; (*b*) R. Chinchilla and C. Nájera, *Chem. Rev*., 2007, **107**, 874.

32 A. D. Creamer, S. D. Dreher and P. J. Walsh, *J. Am. Chem. Soc.,* 2012, **134**, 13765.

33 G. Yin, M. Gao, N. She, S. Hu, A. Wu and Y. Pan, *Synthesis,* 2007, **20**, 3113.

34 (*a*) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.,* 2011, **133**, 13577; (*b*) H.-Q, Do and O. Daugulis, *Org. Lett*., 2009, **11**, 421; (*c*) I. Popov, H.-Q. Do and O. Daugulis, *J. Org. Chem.,* 2009, **74**, 8309.