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Synthesis of *N*-aryl imidazoles catalyzed by copper nanoparticles on nanosized silica-coated maghemite

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ABSTRACT

A magnetically recoverable catalyst consisting of copper nanoparticles (CuNPs) on nanosized silica-coated maghemite is presented. The catalyst has been prepared under mild conditions by mixing the magnetic support with a freshly prepared suspension of CuNPs obtained by fast reduction of anhydrous $CuCl_2$ with lithium sand and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) as electron carrier. This copper-based catalyst has shown to be very efficient in the *N*-(hetero)arylation of imidazole using (hetero)aryl bromides and iodides as arylating agents under ligand-free conditions. The catalyst is easily recovered by means of an external magnet and can be reutilized in three N-arylation cycles without apparent loss of catalytic activity.

1. Introduction

The development of new methodologies for C(aryl)–N(heterocycle) bond formation is of high interest in synthetic organic chemistry, mainly because nitrogen containing heterocyclic moieties are extensively found in natural and synthetic bioactive compounds.[1] In addition, many of these *N*-heterocyclic substructures are used as ligands for transition-metal catalysis,[2] and also in the synthesis of ionic liquids.[3] Among the *N*-aryl derivatives, *N*-aryl imidazoles are often considered as privileged motifs, which play a pivotal role in the synthesis of a broad range of pharmaceutical and agrochemical products; among other properties, they allow soluble salts formation, which is essential for drug bioavailability.

Transition-metal catalyzed cross-coupling between aryl halides and *N*-heterocyclic compounds is arguably the most powerful and broadly accepted tool for the synthesis of *N*-aryl heterocycles.[4] Although palladium[5] and nickel[6] catalysts have proven to be highly efficient in promoting these coupling reactions, in the last decade, economical and environmental considerations have drawn the attention of many research groups to the development of copper-based catalysts to perform these C–N bond forming reactions. Significant contributions to this renaissance of Ullmann-type arylations have been made by the groups of Buchwald,[7] Taillefer,[8] and Ma,[9] among others.[10] Although many of these new methodologies helped to overcome some of the main drawbacks of traditional copper-promoted N-arylation procedures (i.e., harsh conditions, over-stoichiometric amount of copper reagents), most of them involve the use of homogeneous copper catalysts, and even though copper is inexpensive and low metal loading is often sufficient to achieve reasonable conversions, the difficulty in the recovery and reuse of these homogeneous catalysts limit their use, mainly in the synthesis of drug molecules, which must be free of residual metal.

There are few examples in the literature about the use of heterogeneous copper-based catalysts for imidazole N-arylation,[11] and in about half of them aryl boronic acids are employed as aryl donors (Lam–Chan reaction).[11d–f] Although these boronic reagents allow mild reaction conditions, their application is limited by the availability and cost of functionalized boron compounds, and in addition, the atom efficiency of the process is low. On the other hand, copper nanoparticles (CuNPs) as copper source in heterogeneous catalysts for C–N bond formation has scarcely been reported.[12] It is known that, due to their large surface-to-volume ratio, nanosized

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metal particles often exhibit remarkable catalytic properties, showing both higher activities and selectivities compared to that of the bulk metal. These metal nanoparticles have been considered to be on the frontier between the homogeneous and heterogeneous catalysis, preserving the main advantages of both methodologies.[13] However, the separation and recovery of these nanocatalysts from the reaction medium is not always easy due to the nanometric size of the particles that hinders the use of standard separation methods (filtration, centrifugation), thus dispersion of metal nanoparticles over organic or inorganic supports is mandatory to overcome this drawback. In this context, in the last decade nanotechnology has significantly contributed to the development of new magnetic materials for their use as supports in the preparation of magnetic nanocatalysts that can be easily separated from the reaction medium by means of an external magnet.[14] These magnetic nanomaterials used as supports usually consist of core-shell structures in which iron oxides (Fe_xO_y) are commonly used as the magnetic core. Coating of this magnetic core with organic or inorganic polymers prevents undesired agglomeration processes, for this purpose, silica coating is widely used as it improves both chemical and thermal stability of the magnetic nanomaterials and also because it can be easily functionalized for diverse applications.[15] To the best of our knowledge, the only example in the literature about the use of a copper-based magnetic catalyst for the N-arylation of heterocycles is a recent work by Panda et al.[16] who reported on the use of copper ferrite ($CuFe_2O_4$) nanoparticles for the N-arylation of diverse *N*-heterocycles, although only three imidazoles using bromobenzene as arylating agent were tested, and metal leaching (copper and iron) from the catalyst was detected.

On the other hand, in the last years, we have actively been working on the use of nanosized copper-based catalysts for their use in a variety of coupling and cycloaddition reactions.[17] Very recently, we have reported on the preparation of a new magnetic nanocatalyst consisting in copper nanoparticles dispersed on silica-coated maghemite (MagSilica®),[18] which demonstrated to be a very efficient, versatile and reusable catalyst for three important transformations involving terminal alkynes, i.e., the synthesis of 1,3-diynes, the three-component coupling of alkynes, aldehydes and amines for the synthesis of propargyl amines (A^3 coupling), and the 1,3-dipolar cycloaddition reaction of terminal alkynes with in situ generated organic azides for the synthesis of 1,2,3-triazoles. Encouraged by the remarkable performance of this new copper-based nanocatalyst, and prompted by our interest in broadening its synthetic applications, we set out to evaluate its catalytic efficiency in the synthesis of *N*-aryl imidazoles.

2. Results and discussion

2.1. Catalyst preparation and characterization

The CuNPs-based magnetic catalyst was prepared as previously reported by us (see Experimental section for details).[18] Briefly, CuNPs were prepared by fast reduction of anhydrous $CuCl_2$ with an excess of lithium sand and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl in THF at room temperature. Then, the magnetic support (MagSilica) was added and after stirring the resulting suspension for 1 h, the catalyst was filtered, washed and dried under vacuum for 2 h.

The catalyst was characterized by means of transmission electron microscopy (TEM), energy dispersive X-ray (EDX) analysis, powder X-ray diffraction (XRD), temperature programmed reduction (TPR), and inductively coupled plasma atomic emission spectroscopy (ICP-AES). The copper loading fixed to the magnetic support was 6.8 wt % as determined by ICP-AES. The TPR profile of the catalyst showed only one peak, which was assigned to the reduction of copper oxidized species (CuO). The presence of this species indicates that CuNPs have been oxidized during handling of the catalyst under air. Besides, no peaks attributable to the support reduction were detected. The lack of iron species available for reduction strongly suggests that the magnetic core is fully coated by the SiO_2 shell. Energy dispersive X-ray analysis on various regions confirmed the presence of copper, with energy bands of 8.04, 8.90 (K lines) and 0.92 keV (L line). The XRD diffractogram showed the support diffraction pattern, but no diffraction peaks owing to copper species were detected, this could be attributed to the amorphous character of the CuNPs deposited on the support and/or to the existence of crystal domains below 10 nm in size. Analysis by TEM showed the presence of well dispersed spherical nanoparticles on the magnetic support, with a narrow size distribution and an average particle size of 3.0±0.8 nm (Fig. 1).

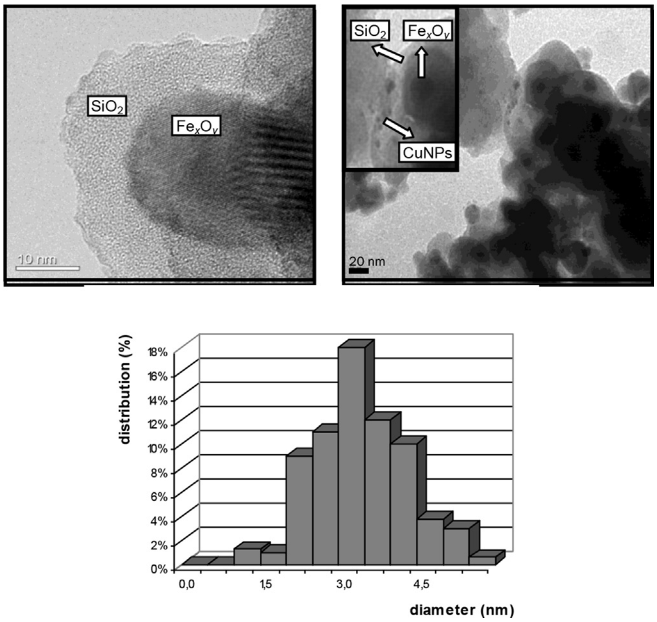
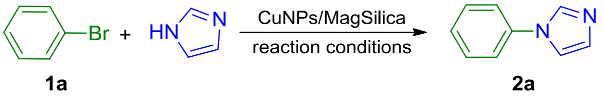


Fig. 1. TEM micrograph of the magnetic support (up left); TEM micrograph of CuNPs/MagSilica catalyst (up right); size distribution graphic of supported CuNPs (bottom). The sizes were determined for 100 nanoparticles selected at random.

2.2. Synthesis of *N*-aryl imidazoles

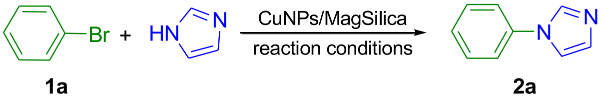
A series of *N*-aryl imidazoles were synthesized under mild conditions by reacting a variety of aryl- or heteroaryl halides with imidazole in the presence of the CuNPs/MagSilica nanocatalyst, under air. For the optimization of the reaction conditions, bromobenzene (**1a**) was chosen as model arylating agent (Scheme 1).



Scheme 1. Optimization of reaction conditions.

We started the optimization of the N-arylation process by reacting bromobenzene (1.0 mmol) with imidazole (1.0 mmol) in the presence of the CuNPs/MagSilica catalyst (100 mg, 11 mol % Cu), in DMF as the solvent and using K_2CO_3 (2.0 mmol) as base. Under these conditions, 1-phenyl-1*H*-imidazole (**2a**) was obtained in 52% yield after 24 h of reaction time at the reflux temperature of DMF (Table 1, entry 1). When the reaction was performed in the absence of any added base the yield decreased to 4% (Table 1, entry 2), thus demonstrating the necessity of the presence of a base for the

Table 1
Optimization of the reaction conditions for the N-arylation of imidazole[a]



Entry	Solvent	Temp (°C)	Base	Time (h)	**2a** Yield %[b]
1	DMF	152	K_2CO_3	24	52
2	DMF	152	—	30	4
3	DMF	152	*tert*-BuOK	24	11
4	DMF	152	DBU	24	2
5	DMF	152	TBAH	24	15
6	Toluene	111	K_2CO_3	20	—
7	THF	66	K_2CO_3	22	12
8	H_2O	100	K_2CO_3	20	—
9	DMSO	189	K_2CO_3	24	42
10[c]	**DMF**	**152**	**K_2CO_3**	**24**	**85** (60)[d] (71)[e] (86)[f]

The bold values signifies the optimum reaction conditions found.

[a] Bromobenzene (1.0 mmol), imidazole (1.0 mmol), base (2.0 mmol), 100 mg of catalyst, in 6 mL of solvent and under air atmosphere, unless otherwise stated.

[b] GLC yield based on the starting bromobenzene.

[c] Reaction performed using 2.0 mmol of imidazole.

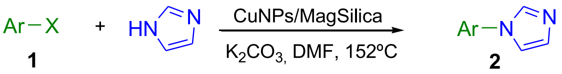
[d] Reaction performed using 50 mg of catalyst.

[e] Reaction performed using 75 mg of catalyst.

[f] Reaction performed using 150 mg of catalyst.

reaction to take place. In view of this observation, we decided to test bases of different nature, where K_2CO_3 proved to be the most effective one (compare entry 1 with entries 3, 4 and 5). Then, the effect of the solvent was studied. As shown in Table 1 (entries 6–9), aprotic polar solvents, such as DMF and DMSO gave better results than protic polar ones (H_2O) or those with lower dipolar moment (toluene, THF). After that, we analyzed the influence of the imidazole/PhBr ratio on the reaction yield, and we observed that a twofold increase in this ratio resulted in a significantly higher yield of the desired *N*-arylated product (Table 1, entry 10). Finally, the optimal amount of catalyst was found to be 100 mg under the reaction conditions (see Table 1, footnotes d and e).

With the optimized reaction conditions in hand, the scope of the catalyst in the N-arylation of imidazole using different arylating agents was evaluated (Scheme 2).



Scheme 2. Synthesis of *N*-aryl imidazoles.

In order to study the effect of the nature of the halide on the reaction course, we first tested different *p*-halotoluenes. As expected, the reactivity followed the order aryl iodide>aryl bromide>>aryl chloride. As shown in Table 2 (entries 2–4), *p*-chlorotoluene (**1d**) was found to be almost unreactive, whereas both *p*-bromotoluene (**1b**) and *p*-iodotoluene (**1c**) gave the corresponding *N*-arylated imidazole **2b** in good yield, **1c** being converted into **2b** at a considerably shorter reaction time. With the aim to take advantage of the lack of reactivity showed by the aryl chlorides, we decided to explore the selectivity of the arylation process by using dihalogenated arylating agents. For this purpose, *p*-chloroiodobenzene (**1e**) and *p*-bromochlorobenzene (**1f**) were reacted with imidazole under the optimized conditions, and we found that **1e** was efficiently converted into the expected chlorinated product **2c** (Table 2, entry 5) whereas **1f** also gave **2c** as the major reaction product but in a markedly lower yield (Table 2, entry 6). This observation led us to further explore the influence of the electronic properties of the aromatic ring of the arylating agent on the course of the C–N coupling reaction. Thus, we tested different aryl bromides and iodides substituted with electron-withdrawing or electron-donating groups. As shown in Table 2, aryl iodides **1g** and **1h** gave the corresponding *N*-arylated products in good yields irrespective of the electronic properties of the substituents attached to the aromatic ring (Table 2, entries 7 and 8). On the contrary, electron poor aryl bromide **1i** showed to be much less reactive than that bearing a strong electron-donating group on the aromatic ring (compare entries 9 and 10 in Table 2). On the other hand, *p*-bromostyrene (**1k**) and 4-bromo-1,1′-biphenyl (**1l**) showed to be as reactive as *p*-bromotoluene (**1b**), leading to the corresponding *N*-arylated imidazoles **2g** and **2h** in good yield (Table 2, entries 11 and 12). Unfortunately, the catalyst showed to be less efficient in the coupling of sterically-demanding arylating agents, such as 1-bromonaphthalene (**1m**), which was converted into 1-(naphthalen-1-yl)-1*H*-imidazole (**2i**) in 55% yield after 60 h of reaction time. In an attempt to extend the scope of our methodology to the use of boronic acids as arylating agents (Lam–Chan reaction), phenyl boronic acid was reacted with imidazole under the optimized conditions leading to 1-phenyl-1*H*-imidazole **2a** in moderate yield (Table 2, entry 14).

On the other hand, we were pleased to find that the N-arylation reaction also proceeded with 2-bromothiophene (**1o**) as arylating agent leading to 1-(thien-2-yl)-1*H*-imidazole (**2j**) in excellent yield as the only reaction product (Table 2, entry 15). Unfortunately, when we applied the same N-arylation process to other *N*-heterocycles, such as pyrrole, indole, pyrazole or benzotriazole, using bromobenzene as arylating agent, the unreacted starting materials were recovered after 24 h of reaction time.

2.3. Recovery and reuse of the catalyst

We selected bromobenzene as model arylating agent for the study of the catalyst performance after various cycles of recovery and reuse. The catalyst could be separated from the reaction medium, washed with solvent and reused very easily, simply with the aid of a permanent magnet placed on the outer wall of the reaction flask, thus minimizing the loss of catalyst, which usually occurs in filtration processes. Fig. 2 shows the recovery process of the catalyst by means of an external magnet, and the catalyst performance for the synthesis of **2a** after three consecutive cycles without significant loss of catalytic activity.

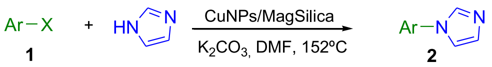
On the other hand, since no copper leaching has been detected by atomic absorption spectrometry in the crude reaction mixture after removal of the catalyst, the N-arylation process is suggested to be heterogeneous in nature. Although, an alternative catalytic process in which the copper supported nanocatalyst could be acting as a reservoir of copper species that leach into the solution and re-adsorb, should not be discarded.[19]

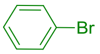
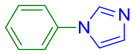
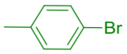
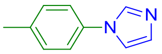
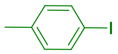
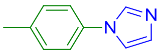
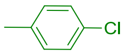
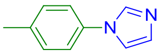
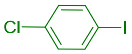
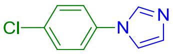
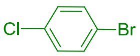
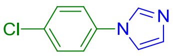
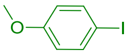
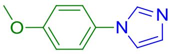
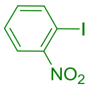
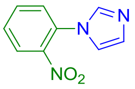
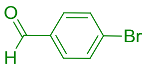
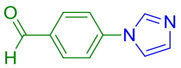
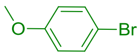
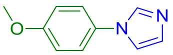
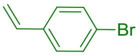
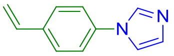
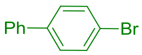
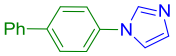
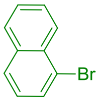
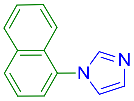
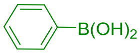
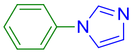
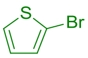
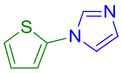
3. Conclusions

We have successfully developed a new methodology for the copper-catalyzed *N*-(hetero)arylation of imidazoles with (hetero) aryl bromides and iodides under ligand-free conditions, using a magnetically recoverable nanocatalyst consisting of copper nanoparticles on nanosized silica-coated maghemite. The catalyst is very stable under the reaction conditions and allow the N-arylation reaction to be conducted under air. The simplicity of the methodology, together with the high atom economy of the process and the easy of recovery and reuse of the catalyst, makes this copper-based magnetic nanocatalyst a very attractive alternative for the synthesis of *N*-(hetero)aryl imidazoles. We are actively exploring other applications of this copper nanocatalyst in synthetic transformations of high interest for the fine chemical industry.

Table 2

Synthesis of *N*-aryl imidazoles catalyzed by CuNPs/MagSilica[a]



Entry	Aryl halide **1**		Reaction time (h)	Product **2**		Yield %[b]
1		**1a**	24		**2a**	80
2		**1b**	22		**2b**	83
3		**1c**	14		**2b**	91
4		**1d**	30		**2b**	10
5		**1e**	18		**2c**	88
6		**1f**	32		**2c**	45[c]
7		**1g**	12		**2d**	93
8		**1h**	18		**2e**	87
9		**1i**	26		**2f**	67
10		**1j**	21		**2d**	90
11		**1k**	20		**2g**	80
12		**1l**	22		**2h**	85
13		**1m**	60		**2i**	64
14		**1n**	30		**2a**	58
15		**1o**	24		**2j**	92

[a] The reactions were conducted under the optimized conditions.

[b] Isolated yield after column chromatography (hexane/ethyl acetate), based on the starting aryl halide.

[c] Together with 10% of the corresponding bis-imidazole product.

4. Experimental section

4.1. General

All moisture sensitive reactions were carried out under a nitrogen atmosphere. Anhydrous tetrahydrofuran was freshly distilled from sodium/benzophenone ketyl. Other solvents were treated prior to use by standard methods.[20] All starting materials were of the best available grade (Aldrich, Fluka, Merck) and were used without further purification. Commercially available copper(II) chloride dihydrate was dehydrated upon heating in oven (150 °C, 45 min) prior to use for the preparation of CuNPs. MagSilica® was provided by Evonik Industries AG (Essen, Germany). Column chromatography was performed with Merck silica gel 60 (0.040–0.063 μm, 240–400 mesh). Thin layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F_{254}, 0.25 mm).

4.2. Instrumentation and analysis

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrometer using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as internal reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. Infrared (FTIR) spectra were obtained on a Nicolet-Nexus spectrophotometer. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a Shimadzu GC-14B instrument equipped with a flame-ionization detector and a 30 m column (HP-5MS, 0.25 mm, 0.25 μm), using nitrogen as

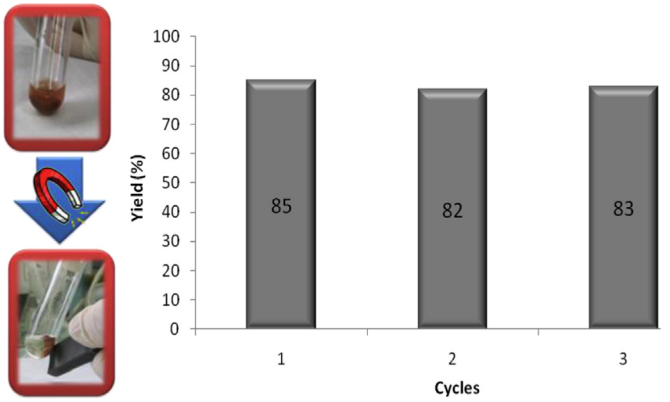


Fig. 2. Recovery of the magnetic catalyst (left), and performance of the catalyst in the synthesis of 1-phenyl-1*H*-imidazole (**2a**) after three consecutive cycles (right).

carrier gas. The freshly prepared catalyst was characterized by Transmission Electron Microscopy (TEM) in a JEOL JEM-2100F-UHR instrument, operated at an acceleration voltage of 200 kV. One hundred metal particles were measured to perform the particle size distribution. Copper content in the supported catalyst was determined by Inductively Coupled Plasma Atomic Emission Spectroscopy (ICP-AES), in a Spectro Arcos instrument. The catalyst specific surface area was measured by BET method, from a N_2 isotherm at 77 K in NOVA 1200e apparatus. The reducibility of the supported catalysts was analyzed by Temperature Programmed Reduction (TPR) in a in-house-made equipment. Before reduction, the samples were treated with flowing Ar at 300 °C. Then, a flowing mixture (20 mL/min) of 10% H_2/Ar was introduced, raising the temperature at 8 °C/min from room temperature up to 550 °C. The TPR profile was obtained following the H_2 consumption with a TCD detector. X-ray diffraction (XRD) analyses were performed using a Bruker AXS D8 Advance diffractometer, equipped with a Cu-Kα1,2 radiation source. Atomic absorption spectroscopy was carried out in a Perkin Elmer AA700 spectrometer.

4.3. CuNPs/MagSilica catalyst preparation

A mixture of lithium sand (21 mg, 3.0 mmol) and 4,4′-di-*tert*-butylbiphenyl (DTBB, 26 mg, 0.1 mmol) in THF (3 mL), was stirred at room temperature under nitrogen atmosphere. When the reaction mixture turned dark green (15 min), indicating the formation of the corresponding lithium arenide, anhydrous $CuCl_2$ was added (134 mg, 1.0 mmol). The resulting suspension was stirred until it turned black (15–30 min), indicating the formation of copper(0) nanoparticles. Then, it was diluted with THF (10 mL) and MagSilica (500 mg) was added. The resulting suspension was stirred for 1 h, and then bidistilled water (2 mL) was added for eliminating the excess of lithium. The resulting solid was filtered under vacuum in a Buchner funnel and washed successively with water (10 mL) and acetone (10 mL). Finally, the solid was dried under vacuum (5 Torr) for 2 h.

4.4. General procedure for imidazole N-arylation reaction

To a vigorously stirred suspension of the CuNPs/MagSilica catalyst (100 mg) in DMF (6 mL) under air, K_2CO_3 (276 mg, 2.0 mmol) and imidazole (136 mg, 2.0 mmol) were added. The reaction mixture was stirred for 30 min and then the corresponding aryl halide (1.0 mmol) was added and the reaction flask was immersed in an oil bath at the reflux temperature of DMF (152 °C). The reaction mixture was stirred at this temperature until no further conversion of the starting aryl halide was observed (TLC, GC). The catalyst was immobilized by means of a permanent magnet placed on the outer wall of the reaction flask, and washed twice with Et_2O (10 mL each). Finally, the catalyst was dried under vacuum (5 Torr) for its recovery and reuse. The crude reaction mixture was evaporated under vacuum (15 Torr) and the resulting residue was purified by flash column chromatography (silica gel, hexane/AcOEt) to afford the corresponding *N*-aryl imidazoles (**2a**–**j**). All known compounds included in Table 1 were characterized by comparison of their chromatographic and spectroscopic data (^1H, ^{13}C NMR, and MS) either with those of the corresponding commercially available pure samples (**2g**) or with those described in the literature (**2a**,[21] **2b**,[21] **2c**,[22] **2d**,[21] **2e**,[11a] **2f**,[11a] **2h**,[23] **2i**,[24] **2j**[25]).

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.04.003.

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