

First Sustainable Aziridination of Olefins Using Recyclable Copper-Immobilized Magnetic Nanoparticles

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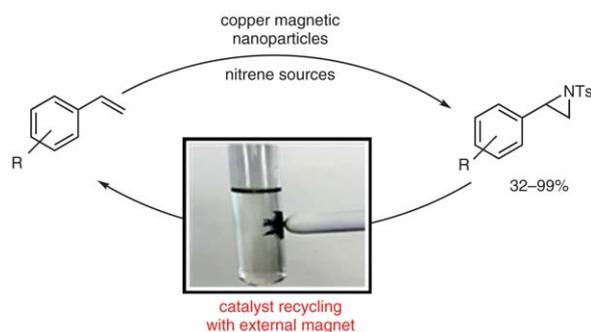
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Abstract The first copper-catalyzed aziridination of olefins using recyclable magnetic nanoparticles is described. Magnetic nanoparticles were modified with dopamine and used as a support to coordinate copper. The methodology was optimized with styrene as olefin and using [N-(p-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) as nitrene source. A microwave irradiation decreased the reaction time by 4-fold compared to conventional heating method. The catalyst was recovered by simple magnetic extraction and could be reused successfully up to five times without significant loss of activity. The methodology was applied to a range of different olefins leading to moderate to excellent yields in the formation of the expected aziridine.

Key words sustainable aziridination, magnetic nanoparticle, copper catalyst, nitrene insertion

Insertion of nitrogen atom to an organic scaffold has arisen as a fundamental step in organic synthesis. Valuable tools, such as nitrene insertion onto Csp³–H bonds or alkenes, *via* direct C–H amination or through aziridination, had been developed.^{1–5} Particularly in the case of aziridine rings, great biological interest as potential therapeutic and cytotoxic agents, make them an attractive synthetic targets.^{6–8}

Originally upon thermic or ultrasonic activation,^{9,10} alkene aziridination through metal-assisted catalysis has emerged as the most efficient, selective, and reliable methodology.^{4,5,11} Copper as metal catalyst^{12,13} and hypervalent iodine as oxidant^{14,15} are the most popular conditions to afford such three-membered rings in good efficiency.¹⁶

Nevertheless, there are still weaknesses to spread this methodology to an industrial scale. A literature survey revealed that copper catalytic charge is generally high while the tolerance to functional groups remains moderate. Furthermore, homogeneous catalytic systems present draw-

backs, such as stability, separation, and recovery, which are not well-suited for sustainable chemistry. Moreover, the copper counterion could cause dramatic damage or is strongly harmful for the environment (*i.e.*, PF₆⁻). Finally, the recycling of the metal is often obscured and only few researches have been engaged toward catalyst recycling. To circumvent all these concerns, recoverable catalytic systems had been depicted by supporting the metal on organic or inorganic materials, such as zeolite, alumina or multi-walled carbon nanotubes.¹⁷ For example, a heterogeneous catalyst was designed by insertion of copper(II) ligand complex inside Y zeolite pores.^{18–20} The catalyst may be reused by filtration and/or centrifugation. Copper supported by alumina was also used for the aziridination but limitations such as tedious catalyst preparation, low yields, and long reaction times reduce its efficiency.^{21,22} Moreover, the procedures related to these supported catalysts usually used a large excess of sometimes hardly obtained olefins toward a stoichiometric amount of the cheap PhI=NTs as a limiting reagent.

Otherwise, thanks to their ease of recovery, magnetic nanoparticles (MNP) have become more and more attractive to support organic or inorganic catalysts. Examples with Fe₃O₄ grafted with the robust and stable dopamine to coordinate metals²³ were successfully reported for oxidation,²⁴ hydrogenation,²⁵ or Suzuki coupling reactions.²⁶ Nevertheless, the use of modified MNP with copper as heterogeneous supported catalysts for aziridination was never reported yet.

Herein, we report the first use of copper-loaded MNP to catalyze conversion of alkenes into the corresponding aziridines. Consequently, Cu(OTf)₂ or CuPF₆ complexes were changed for magnetic Fe₃O₄-dopamine-Cu, and the as-obtained optimized conditions were used for the conversion of various olefins.

MNP-supported Cu catalyst (Fe_3O_4 -Dopa-Cu) were readily prepared from inexpensive starting materials *via* a simple method as a heterogeneous magnetic catalyst.²⁷ For this, dopamine hydrochloride was added to an aqueous solution of Fe_3O_4 by sonicating for 2 h. Expected MNP were obtained through addition of 10 wt% of CuCl_2 in the presence of hydrazine and sodium borohydride (NaBH_4) as reducing agents. Characterization of the materials were performed using transmission electron microscopy (TEM), atomic absorption spectroscopy (AAS), X-ray diffraction (XRD), and FT-IR spectroscopy. As shown by TEM images and confirmed by XRD (see Supporting Information), 11 nm sized spherical highly crystalline Fe_3O_4 nanoparticles were obtained by coprecipitation of iron salts. Anchoring of dopamine, proved by FT-IR, and subsequent complexation with copper did not affect the morphology, size, and crystallinity of the magnetic nanoparticles. Copper loading was measured by AAS as 10%. Copper particles were not visible neither in TEM images nor in XRD analyses that tend to prove that atomic copper was deposited. Efficiency of the as-obtained catalyst was evaluated in classical conditions for the aziridination of styrene (Table 1). As a reference, $\text{Cu}(\text{OTf})_2$ was tested using two different oxidants. Portionwise addition of $\text{PhI}=\text{O}$ resulted in good conversion (monitored by TLC) and yield whereas $\text{PhI}(\text{OAc})_2$ gave poor results (Table 1, entries 1 and 2).^{14,16} CuPF_6 was also tested (result not shown) and, as expected, gave similar yield to $\text{Cu}(\text{OTf})_2$. Copper complexes were substituted with Fe_3O_4 -Dopa-Cu. First attempt was realized by mixing $\text{PhI}=\text{O}$ with tosylamine in dry acetonitrile with 4 Å molecular sieves (Table 1, entry 3). The reaction succeeded in the formation of the expected aziridine but the yield was low (27%) because of a problematic recovering of magnetic catalyst. According to Kolotilov,²⁸ a covalent bonding between Fe_3O_4 and silica from molecular sieves could happen, causing hard recoverability and low activity of catalyst. To overcome this side interaction, we changed the oxidant by the preformed intermediate [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane ($\text{PhI}=\text{NTs}$)²⁹ that does not require molecular sieves. We were pleased to obtain the expected product but flanked with a low yield of 18% under these conditions (Table 1, entry 4). Hopefully, we succeeded in easily recovering the catalyst using an external magnet.

In view of this promising result, we investigated several parameters such as temperature, time, equivalent of reagent, and amount of catalyst in order to optimize the reaction conditions and enhance catalytic activity.

Under conventional heating (CH), a simple change of the temperature from 40 °C to 70 °C allowed a threefold increase of the yield, from 18% to 70% (Table 1, entry 5). Longer reaction time resulted also in an improvement of the aziridination outcome to 82% and 86% after 1 h and 2 h (Table 1, entries 6 and 7). We also tried to reduce the amount of $\text{PhI}=\text{NTs}$ from 1.4 equiv. to 1.2 equiv. and 1 equiv.

Table 1 Alkene Aziridination Using MNP Catalyst

Entry	Oxidant	Copper source ^a	Time (h)	Temp (°C)	Yield (%) ^b
1	$\text{PhI}(\text{OAc})_2$ 1.4 equiv. ^c	$\text{Cu}(\text{OTf})_2$	18	0	21
2	$\text{PhI}=\text{O}$ 1.4 equiv. ^c	$\text{Cu}(\text{OTf})_2$	6	0	93
3	$\text{PhI}=\text{O}$ 1.4 equiv. ^c	Cu-MNP	6	0	27
4	$\text{PhI}=\text{NTs}$ 1.4 equiv.	Cu-MNP	0.5	40	18
5	$\text{PhI}=\text{NTs}$ 1.4 equiv.	Cu-MNP	0.5	70	70
6	$\text{PhI}=\text{NTs}$ 1.4 equiv.	Cu-MNP	1	70	82
7	$\text{PhI}=\text{NTs}$ 1.4 equiv.	Cu-MNP	2	70	86
8	$\text{PhI}=\text{NTs}$ 1.2 equiv.	Cu-MNP	2	70	90
9	$\text{PhI}=\text{NTs}$ 1 equiv.	Cu-MNP	2	70	64
10	$\text{PhI}=\text{NTs}$ 1.2 equiv.	Cu-MNP	2 ^d	70	91
11	$\text{PhI}=\text{NTs}$ 1.2 equiv.	Cu-MNP	0.5 ^d	70	87

^a 0.1 equiv. of 10% Fe_3O_4 -Dopa-Cu catalyst.

^b Determined after purification on silica gel.

^c TsNH_2 (1.4 equiv.) was added.

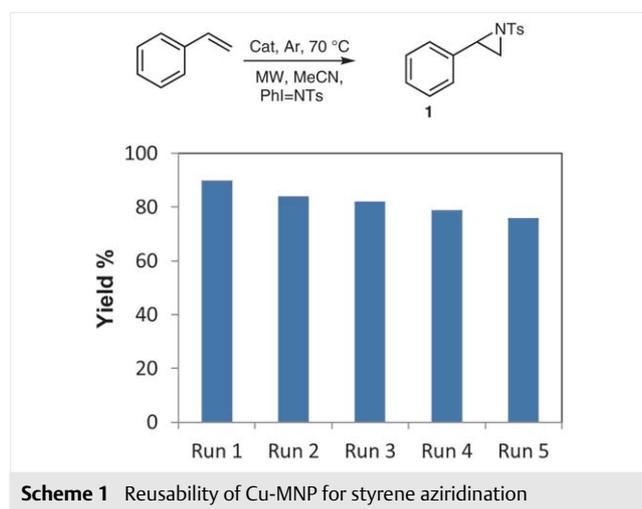
^d MW irradiation.

(Table 1, entries 8 and 9). At least, we were able to obtain a comparable yield with our recyclable catalyst (90%, Table 1, entry 8) than those obtain in literature under classical conditions ($\text{PhI}=\text{NTs}$, $\text{Cu}(\text{OTf})_2$).¹⁶

We also investigated different optimization parameters such as solvent, copper loading on MNP, and catalyst charge in the media and MW irradiation.^{30,31} Changing acetonitrile to other common solvent (water, acetone, dichloromethane, THF) resulted in a large decrease or a total lack of reactivity (see Supporting Information). Modifying copper amount on MNP (from 10% to 1%) or catalytic charge (from 10% to 1%) did not change reaction behaviors and leaching (see Supporting Information). Fortunately, under microwave irradiation (MW), we were pleased to observe full conversion and 91% yield in 2 h (Table 1, entry 10). Moreover, MW irradiation could reduce by four times the reaction duration compared to CH, and 87% of aziridine were achieved in 30 min (Table 1, entry 11). Nevertheless, an atomic absorption spectroscopy (AAS) analysis revealed a copper leaching of 20% during the experimentation carried out using the best found conditions. We postulated that competitive interac-

tion between Cu-dopamine immobilized on the surface of catalyst and other nitrogen sources such as excess of PhINTs or even the product itself could occur and potentially can be a reason of Cu leaching from Fe₃O₄-Dopa-Cu system.³²

The lifetime of the catalyst and its level of reusability were tested by carrying out turnover reactions on the same batch of catalyst in aziridination reaction of styrene (Scheme 1). All reactions were performed under the same conditions. The results showed that the Fe₃O₄-Dopa-Cu magnetic catalyst could be reused up to five times with full conversion of styrene, good yield, and slight loss of activity. Also, it should be mentioned that after five runs, no loss of magnetic responsiveness or morphological change was detectable.



Scheme 1 Reusability of Cu-MNP for styrene aziridination

Metal leaching has been measured by AAS analysis after each experience and finally after five runs. Analysis showed there was a leaching of copper from 10 wt % to 4.4 wt % after five reactions. Deeper investigations showed that, after extraction of the catalyst with the magnet, copper traces were detected with the product in the corresponding proportion that has been lost by the catalyst.

A range of olefins was tested toward aziridination using Fe₃O₄-Dopa-Cu catalyst. In general, products were obtained in good to excellent yields (Table 2). Vinyl toluene derivatives gave very good results (Table 2, entries 1–3), especially for the *ortho* substituted. *trans*-Stilbene or *trans*-chalcone suffer from low conversion since 40% and 80% of starting materials were converted (Table 2, entries 4 and 5) but they gave relatively good selectivity (80% and 50%, respectively). When an electron-withdrawing group (EWG), such as chlorine or a nitro group, were added, olefins provided the corresponding aziridines in excellent yields (96% and 91%), respectively (Table 2, entries 6 and 7). Interestingly, in the case of 4-aminostyrene, aziridination did not undergo, probably due to side interactions with catalyst (Table 2, entry 8). However, reaction of protected amine group pro-

ceeded sluggishly and required more than 2 h for completion but afforded the expected product in 78% yield (Table 2, entry 9). This result confirms our suspicions and could explain copper leaching. Indeed, a detrimental interaction with a Lewis base present in the media (*i.e.*, aniline) could be at play and interferes with coordination between the copper and the MNP (generating the leaching by this way). When nitrogen reactivity was reduced using a deactivating protecting group, aziridination took place normally and full conversion was obtained. More functionalized olefin like

Table 2 MW-Assisted Aziridination of Olefins Using Fe₃O₄-Dopa-Cu Catalyst^a

Entry	Substrate	Yield (%) ^{b,c}	Conv. (%) ^d
1		70	>95
2		78	>95
3		83	>95
4		32 (80)	40
5		40 (50)	80
6		96	100
7		91	>95
8		0	>95
9		78	>95
10		0	>30
11		32 (80)	40

^a Conditions: substrate (1 equiv.), PhI=NTs (1.2 equiv.), Cu-MNP (0.1 equiv.), MeCN, 2 h, 70 °C.

^b Recovered by column chromatography.

^c Selectivity is given in bracket.

^d Determined with respect to the crude NMR.

cinnamic derivative was also tested and led to degradation (Table 2, entry 10). Finally, inactivated olefin such as methyl oleate gave promising results since 32% yield was observed with only 40% conversion (80% based on recovered starting materials, Table 2, entry 11).

We have developed an eco-friendly protocol for aziridination reaction using a magnetically recoverable Fe₃O₄-dopamine-Cu catalyst.³³ Optimization led us to use PhINTs under microwave irradiation to give high yield of aziridine. The easy recyclability of the catalyst with a simple magnet allowed it to be reused for five times without significant loss of conversion and yield. Finally, a range of olefins were examined resulting in a medium to excellent yields. Currently, we are investigating the use of different linkers for a better anchoring and chelation of the copper to decrease leaching during the reaction.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0037-1611717>.

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- (33) **General Synthetic Procedure for Aziridination**
To a mixture of olefin substrates (0.4 mmol), 10% Fe₃O₄-Dopa-Cu catalyst (0.04 mmol, 0.1 equiv.) in dry acetonitrile was added PhI=NTs (0.48 mmol, 1.2 equiv.) portionwise in 5 times in microwave at 70 °C under argon atmosphere, and the whole mixture was stirred until TLC showed a complete conversion (10 min to 3 h). The catalyst was removed with an external magnet and washed with dried MeCN. The solvent was removed under reduce pressure. The crude was purified by flash chromatography on silica gel using a Reveleris™ Flash System.