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A Click Strategy for the Immobilization of MacMillan Organocatalysts onto Polymers and Magnetic Nanoparticles

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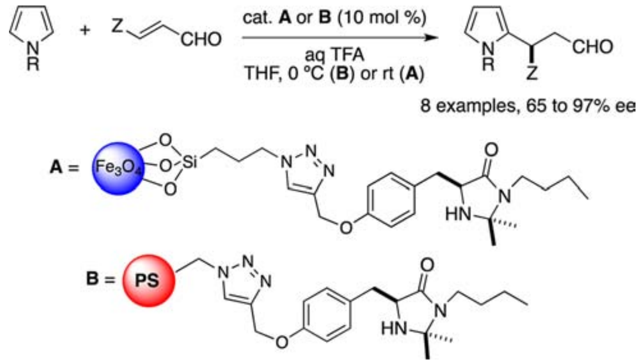
ABSTRACT



A chemically modified, first generation MacMillan imidazolidin-4-one has been anchored onto 1% DVB Merrifield resin and Fe_3O_4 (5.3 ± 1.4 nm) magnetic nanoparticles through copper-catalyzed alkyne azide cycloaddition (CuAAC) reactions. The resulting immobilized catalysts have been successfully used in the asymmetric Friedel−Crafts alkylation of *N*-substituted pyrroles with α,β-unsaturated aldehydes. The PS-supported catalyst (B) showed higher catalytic activity and enantioselectivity, while the MNP-supported one (A) showed higher recyclability and could be used in a sequential process with intermediate magnetic decantation.

Organocatalysis has become one of the most active research areas in asymmetric organic synthesis.[1] However, its practical applications are often limited by factors such as high catalyst cost, the requirement of high catalyst loadings, and difficulties in catalyst recovery and reuse. To avoid these limitations, the immobilization of organocatalysts onto solid supports[2] such as polymers,[3] mesoporous materials,[4] or magnetic nanoparticles[5] leading to asymmetric catalysis under heterogeneous conditions has emerged as a promising strategy.

The enantiopure imidazolidin-4-one derived from phenylalanine *N*-butylamide and acetone (the first generation MacMillan catalyst) is one of the most versatile organocatalysts and has been used with success in a large variety of enantioselective reactions, such as the Diels−Alder reaction,[6] 1,3-dipolar cycloadditions,[7] and Friedel−Crafts

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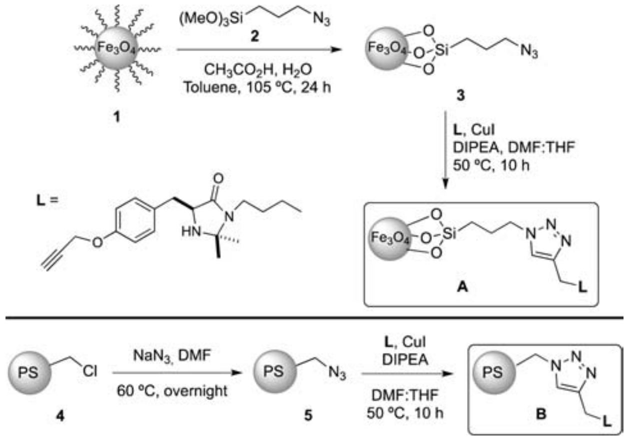
alkylation[8] among others.[9] The heterogenization of this species has also received considerable attention, and examples of the covalent inmobilization of the MacMillan catalyst on different solid organic (JandaJel,[10] polystyrene,[11] liquid crystals[12]) and inorganic[13] materials have been reported in the literature. These immobilized species have almost exclusively been applied in Diels–Alder reactions, while its possible use in asymmetric Friedel–Crafts (F–C) alkylation reactions[14] has remained almost completely unexplored.[15]

In recent years we have successfully used the copper-catalyzed alkyne azide cycloaddition (CuAAC) reaction[16] as a tool for the covalent immobilization of catalytic ligands[17] and organocatalysts onto polystyrene resins (PS)[18] and magnetic nanoparticles (MNPs)[19] and have shown that the 1,2,3-triazole linkers exert highly beneficial effects on the performance of supported organocatalysts in both enamine and iminium mediated processes.[18]

Scheme 1. Immobilization of the First Generation MacMillan Catalyst through CuAAC Reactions



As a continuation of these efforts, we report in this communication the immobilization of the first generation MacMillan catalyst onto slightly cross-linked (1% DVB) Merrifield resin and superparamagnetic Fe_3O_4 nanoparticles using CuAAC reactions and the use of the resulting species as recyclable catalysts for the enantioselective F–C alkylation of *N*-substituted pyrroles with α,*β*-unsaturated aldehydes via iminium intermediates.

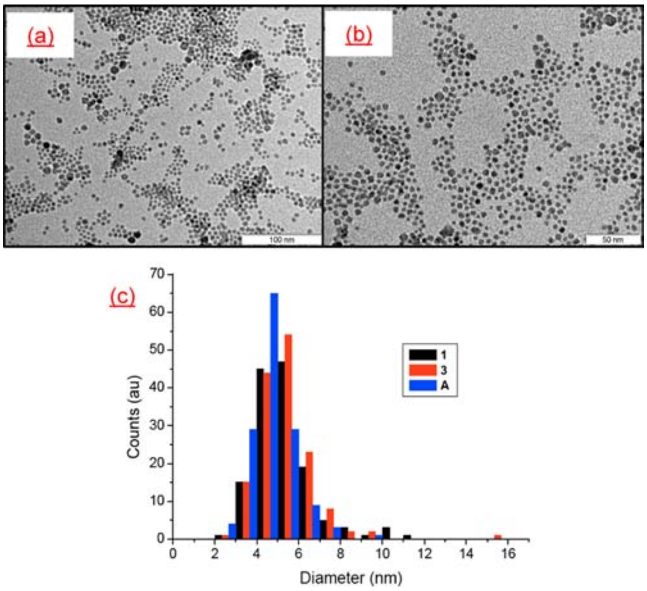


Figure 1. Micrographs and size distribution of MNPs analyzed by TEM. (a) MNPs (**1**), (b) MNPs supported imidazolidinone (**A**), and (c) size distribution of the MNPs.

The target catalysts **A** and **B** were easily prepared by the procedures outlined in Scheme 1. The Fe_3O_4 MNPs **1** used as support were prepared by thermal decomposition of iron(III) acetylacetonate in the presence of oleic acid, oleylamine, and 1,2-dodecanediol as surfactants[20] and showed a narrow size distribution (5.3 ± 1.4 nm). Grafting with 3-(azidopropyltrimethoxy)silane (**2**) afforded the azide functionalized MNPs (**3**),[19] and incorporation of the propargyloxy-substituted imidazolidinone **L** through a

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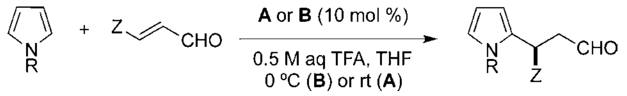
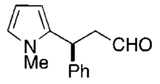
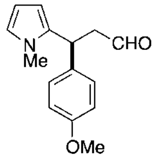
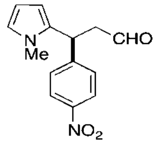
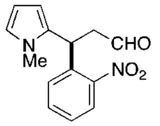
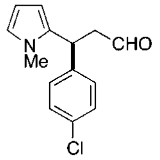
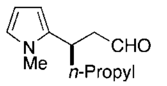
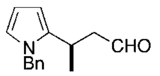
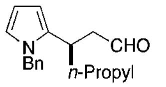
CuAAc reaction led to catalyst **A** (Scheme 1, top). Transmission electron microscopy (TEM) (Figure 1) showed that the size of the MNPs remained practically unchanged over the whole synthetic sequence, and no agglomeration phenomena could be observed.

Following a similar approach, commercially available Merrifield resin (1% DVB, $f = 1.3$ mmol·g^{-1}) was converted to azidomethylpolystyrene,[17a] and organocatalyst **L** was immobilized through a CuAAC reaction to afford catalyst **B** (Scheme 1, bottom). The functionalization level of both catalysts was determined by elemental analysis of nitrogen as 0.34 mmol·g^{-1} (**A**) and 0.91 mmol·g^{-1} (**B**).

The use of functional materials **A** and **B** in the Friedel–Crafts alkylation of *N*-substituted pyrroles with α,β-unsaturated aldehydes was next studied. The reaction between *trans*-cinnamaldehyde and *N*-methylpyrrole (see Supporting Information (SI) for details) was used for the optimization of reaction conditions. Working in THF–H_2O, catalyst **B** gave the best results at 0 °C. The performance of catalyst **A**, in turn, was rather independent from the reaction temperature, and reactions mediated by this species could be conveniently carried out at rt. The results obtained in the F–C alkylation of *N*-methyl and *N*-benzylpyrrole with a representative family of enals have been summarized in Table 1.

Table 1. Friedel–Crafts Alkylation of *N*-Substituted Pyrroles with α,β-Unsaturated Aldehydes[a]



entry	catalyst	time [h]	product	yield [%][b]	ee [%][c]
1	**B**	12		65	93
2	**A**	24		48	77
3	**B**	24		45	81
4	**A**	48		31	68
5	**B**	24		75	94
6	**A**	48		60	81
7	**B**	48		81	97
8	**A**	48		80	91
9	**B**	24		71	91
10	**A**	48		69	71
11	**B**	4		75	92
12	**A**	12		71	79
13	**B**	12		98	79
14	**A**	12		98	65
15	**B**	12		60	88
16	**A**	48		13	n.d.

[a] *N*-Substituted pyrrole (1.25 mmol), aldehyde (0.25 mmol), catalyst (10 mol %), TFA 0.5 M (10 mol %), H_2O (0.054 mL), THF (0.350 mL). [b] Isolated yield. [c] By chiral GLC.

As it can be seen, the polystyrene-based catalyst **B** leads in all the studied cases to higher yields and enantioselectivities in shorter reaction times than the nanoparticle-based catalyst **A**. However, as we will see later, this last catalyst offers important practical advantages derived from its ready separation by magnetic decantation.

When the influence of the α,β-unsaturated aldehyde alkylating agent on the performance of the reaction is analyzed, some trends can be clearly observed: (a) Both β-alkyl and β-aryl substituted enals are appropriate substrates for the reaction; (b) among β-aryl substituted enals, those bearing electron-withdrawing groups lead to the highest yields and enantioselectivities; and (c) other things being equal, more sterically congested substrates lead to higher enantioselectivity.

When supported catalysts **A** and **B** are compared with the homogeneous, first generation MacMillan catalyst (*N*-methyl),[8a] important practical advantages of the heterogeneized species become evident; thus, while the homogeneous catalyst requires reaction temperatures from −60 to −30 °C, **A** and **B** can be used at rt or 0 °C, respectively, with much shorter reaction times. Most notably, the enantioselectivities depicted by the homogeneous MacMillan catalyst (91% mean ee)[8a] and **B** (89.5% mean ee) are essentially identical in spite of the differences in reaction temperature.

The major practical advantage offered by heterogenized catalysts in comparison with their homogeneous counterparts is its easy separation from the reaction medium for recycling and reuse. While polystyrene resins can be readily separated by filtration, superparamagnetic Fe_3O_4 nanoparticles can be easily and quantitatively recovered by magnetic decantation. In the present instance, we studied the possibility of recycling and reusing catalysts **A** and **B** in the reaction of *N*-methylpyrrole with *trans*-cinnamaldehyde (Figure 2). After each cycle, the catalysts were treated with equimolar amounts of 0.5 M TFA solution in order to reactivate the catalyst. We were pleased to observe that both catalysts **A** and **B** could be reused for six consecutives runs (24 h reaction time for **B** and 48 h reaction time for **A**). For catalyst **A**, the initial activity is retained until the fifth cycle, while, for catalyst **B**, a decrease in yield was observed after the third run. Very interestingly, enantioselectivity remains essentially unchanged for both catalysts over the six reaction cycles. Leaching of the functional monomers

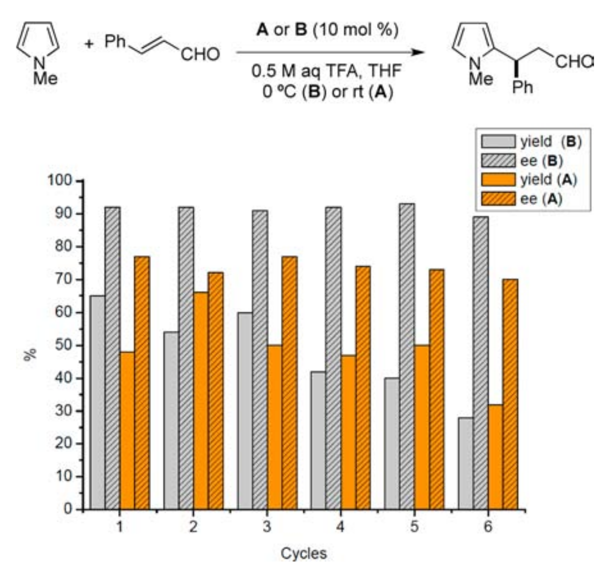
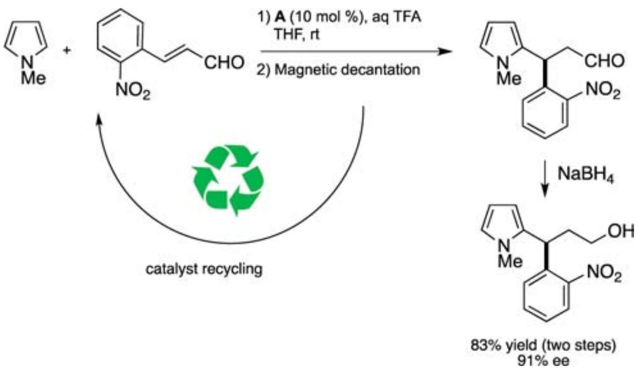


Figure 2. Recycling and reuse of catalyst **A** or **B**.

during the recycling can be almost completely excluded, since elemental analysis after six cycles indicated a functionalization almost identical to the initial ones ($f = 0.27$ gmmol^{-1} for **A** and $f = 0.86$ gmmol^{-1} for **B**). In addition, any significant agglomeration phenomenon in **A** during the recycling could be excluded by TEM after the sixth run (see SI). According to these observations, the decrease of activity in catalyst **B** during recycling can be probably attributed to partial structural collapse of its rather fragile gel structure with repeated use, making part of the catalytic sites unavailable to reagents. This phenomenon would not affect the more robust nanoparticles **A**.

The magnetic nature of catalyst **A** offers practical advantages for its application to complex sequences. We have represented in Scheme 2 two such examples, where the alkylation of *N*-methylpyrrole with (*E*)-3-(2-nitrophenyl)-propenal mediated by **A** is performed, the catalyst is concentrated at the walls of the reaction flask by application of a magnet once the F–C reaction is complete, and the adduct is further transformed by selective reduction with $NaBH_4$ (83% overall yield, 91% ee).[21] In addition, the catalyst could be redispersed in THF and reused in the F–C alkylation without an appreciable decrease in its performance.

Scheme 2. Use of Catalyst **A** in a Sequential Process with Intermediate Magnetic Decantation



In conclusion, we have reported for the first time the immobilization of the first generation MacMillan catalyst onto a polystyrene resin and Fe_3O_4 magnetic nanoparticles using a CuAAC strategy. The resulting functional materials have been successfully used as catalysts in the Friedel–Crafts alkylation of *N*-substituted pyrroles with α,*β*-unsaturated aldehydes. The best results were obtained with the PS-supported imidazolidinone, but the catalyst supported onto MNPs showed more stability in the recycling tests and, thanks to its facile separation from the reaction medium through magnetic decantation, could be used in sequential processes without isolation of the intermediate F–C adduct.

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Supporting Information Available. Experimental details, spectroscopic data of F–C adducts, NMR spectra, and GC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Ee was determined by GLC at the level of the intermediate aldehyde (50–170 °C/1 °C min^{-1}, 1.5 mL/min): *R* isomer t_r = 156.96 min and *S* isomer t_r = 161.24 min.

The authors declare no competing financial interest.