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Research paper

Magnetic Fe_3O_4 nanoparticles bearing Cu^I-NHC complexes by an "auto-click" strategy

Kévin Fauché, Federico Cisnetti *

Université Clermont Auvergne, CNRS, SIGMA Clermont, ICCF, F-63000 Clermont-Ferrand, France

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ABSTRACT

Two copper(I)–NHC complexes bearing an azide group were reacted with alkyne-decorated magnetic Fe_3O_4 nanoparticles without the use of an external copper source. In the case of the least sterically congested complex, the resulting nanoparticles displayed a catalytic activity in copper-catalyzed azide alkyne cycloaddition and some reusability highlighting the covalent grafting of the molecular catalyst by this mild and simple strategy.

1. Introduction

N-heterocyclic carbene complexes are nowadays a tool for the chemist of great significance, among others in the field of catalysis by metal complexes [1,2]. In the recent years, there has been a strong effort towards the heterogenization of molecular catalysts based on *N*-heterocyclic carbene complexes, although this endeavor is met with high challenges. Among the heterogeneous systems actively considered, magnetic nanoparticles (MNPs) attract a considerable interest due to their facile separation from a reaction mixture by the use of an external magnet [3,4]. Several examples of covalent grafting of metal NHC complexes on magnetic nanoparticles have been reported in the recent years [5–14].

Copper-catalyzed azide-alkyne cycloaddition (CuAAC) is one of the most ubiquitous reactions for novel developments in diverse areas ranging from polymers to medicinal chemistry [15]. Copper(I) NHC complexes allow this reaction (see references [13;14] for the use of copper NHC grafted on nanoparticles as CuAAC catalysts), along with other important catalytic transformations [16]. Moreover, although not as widespread as the same reaction from their silver(I) counterparts, the transmetalation from Cu^I-NHC complexes allows the access to other metal-NHC compounds (Au, Pd…) [17]. In the past years, it has been shown that copper(I) NHC complexes bearing one or two azide groups were able to catalyze their own functionalization in solution with an alkyne reagent without any other reactant or catalyst, albeit in an intermolecular manner [18–20]. Due to the simplicity of this 'click' [21] reaction and its suitability to heterogeneous conditions [15,22], we decided to preliminarily explore its potential for the functionalization of magnetic nanoparticles bearing alkyne groups [23] and the use of the resulting nanoparticles in catalysis of the azide-alkyne cycloaddition reaction. In the design of this study, we reasoned that the fact that the functionalization reaction is conducted with dissolved azide-tagged NHC complexes and no other reactant besides the nanoparticles ensures any catalytic activity is to be ascribed to immobilized complexes and not to undissolved impurities. This might constitute an asset in comparison to more conventional strategies in which complexes or ligands react in the presence of other reagents with a functionalized surface bearing the complementary function. To this end, we selected two NHC complexes with a different shape and steric crowding around the metal center: **C1** and **C2** and examined first their reactivity towards alkyne-functionalized MNPs, then the reactivity of the resulting nanocatalysts towards the azide-alkyne cycloaddition as a proof of concept of our novel immobilization strategy (Scheme 1).

2. Experimental section

2.1. Synthesis of the copper complexes

The ligand precursors **L1**·HCl and **L2**·HCl were prepared by adapting a previously reported procedure [19] (see ESI for details).

Procedure for the synthesis of copper complexes:

The imidazolinium salt **L**·HCl (2 mmol, 1 eq.) was suspended in water (20 mL). CuCl (238 mg, 2.4 mmol, 1.2 eq) was added and the resulting suspension was degassed with argon. Aqueous ammonia (14.2

* Corresponding author.
E-mail address: federico.cisnetti@uca.fr (F. Cisnetti).

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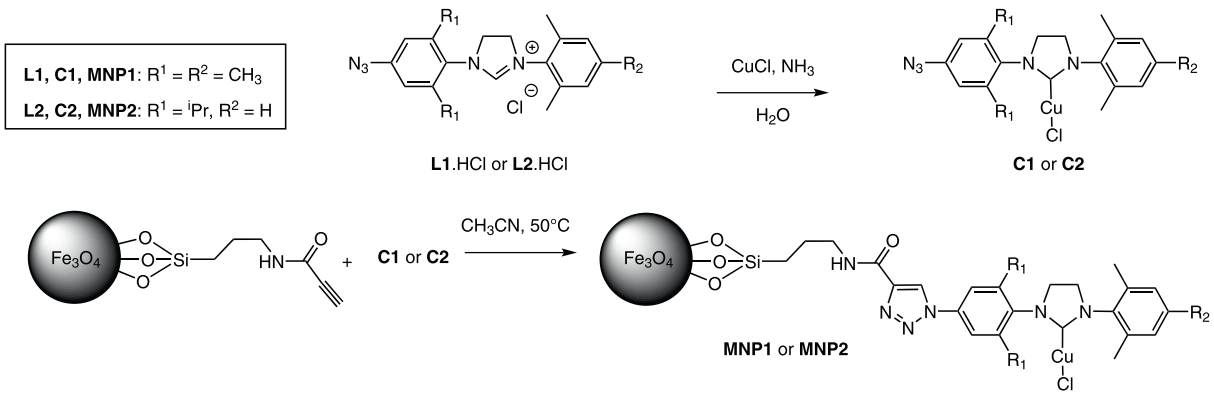


Scheme 1. Azide-tagged NHC complexes and synthesis of heterogenized nanocatalysts.

mol/L as determined by acidimetric titration, 0.85 mL, 12 mmol, 6 eq.) was added, the reaction vessel was degassed for one more minute and the mixture was stirred at room temperature for 1 h. After completion, an extraction with dichloromethane (3 × 20 mL) was performed. The product was dried over anhydrous Na_2SO_4 and Na_2CO_3 and condensed under vacuum.

Work-up for **C1**: the crude product was dissolved in ~5 mL dichloromethane (previously treated with Na_2CO_3) and recrystallized by the dropwise addition of *n*-pentane (~30 mL). The resulting solid was filtered and washed with *n*-pentane. The recrystallization was repeated a second time giving pure **C1** (418 mg, 48% yield). ^{1}H NMR ($CDCl_3$) δ = 6.98 (s, 2H, H_{Ar}), 6.93 (s, 2H, H_{Ar}), 3.7 (broad, 4H, CH_2), 2.36 (s, 6H, *o*-CH_3), 2.32 (s, 9H, *o*-CH_3, *p*-CH_3). ^{13}C NMR (DMSO–d_6) δ = 202.7 ($C_{carbene}$), 140.0 (C_{Ar}), 138.7 (C_{Ar}), 137.8 (C_{Ar}), 135.2 (C_{Ar}), 134.7 (C_{Ar}), 134.3 (C_{Ar}), 129.7 (CH_{Ar}), 119.3 (CH_{Ar}), 51.0 (CH_2), 50.8 (CH_2), 21.0 (CH_3), 18.2 (CH_3), 18.0 (CH_3). ESI-HRMS: calcd. for ($C_{20}H_{23}ClCuN_5$ - Cl + MeCN)$^+$: 437.1510, found: 437.1513; calcd. for ($C_{23}H_{29}ClCuN_5$ – CuCl + H)$^+$: 334.2026, found: 334.2023. CHN Microanalysis calcd. C: 55.55, H: 5.36, N:16.20; found C: 55.39, H: 5.46, N:16.01.

Work-up for **C2**: the crude product was suspended in EtOH and stirred for 30 min. The resulting solid was filtered and washed with EtOH giving pure **C2** (650 mg, 69% yield). ^{1}H NMR (acetone–d_6) δ = 7.28–7.19 (m, 3H, H_{Ar}), 7.02 (s, 2H, H_{Ar}), 4.29–4.15 (m, 2H, CH_2), 4.04–3.98 (m, 2H, CH_2), 3.26 (hept, 2H, J = 6.9 Hz, CH), 2.42 (s, 3H, $CH_{3,Me}$), 1.37 (d, 6H, J = 6.9 Hz, $CH_{3,iPr}$), 1.35 (d, 6H, J = 6.9 Hz, $CH_{3,iPr}$). ^{13}C NMR (DMSO–d_6), δ = 200.8 ($C_{carbene}$), 148.9 (C_{Ar}), 140.4 (C_{Ar}), 137.7 (C_{Ar}), 135.8 (C_{Ar}), 131.7 (C_{Ar}), 128.7 (CHar), 128.6 (CH_{Ar}), 115.0 (CH_{Ar}), 53.5 (CH_2), 50.7 (CH_2), 28.2 (CH), 24.7 (CH_3), 23.2 (CH_3), 17.4 (CH_3). IR (neat): ν (cm^{-1}) = 2960, 2099, 1595, 1481, 1472, 1341, 1323, 1265, 1252, 880. ESI-HRMS: calcd. for ($C_{23}H_{29}ClCuN_5$ - Cl + MeCN)$^+$: 479.1979, found: 479.1981. CHN Microanalysis calcd. C: 58.09, H: 6.36, N:14.73; found C: 58.08, H: 6.21, N:14.62.

2.2. Auto-Click reaction with alkyne-bearing nanoparticles

In a 5 mL round bottom flask, 50 mg of complex **C1** or **C2** were dissolved in 2 mL of acetonitrile. 100 mg of alkyne-bearing nanoparticles prepared following a protocol by Gun'ko *et al.* [23] (see details in ESI) were added. The resulting suspension was sonicated for 6 h. After magnetic decanting of the product, the supernatant was removed and the product was washed with acetonitrile (2 × 2 mL) with 10 min in the ultrasonic bath for each washing. The nanoparticles were dried in vacuo, giving 105 mg of **MNP1** or 95 mg of **MNP2**.

2.3. Catalysis experiments

1 mmol of benzyl azide, 1 mmol of alkyne and 20 mg of **MNP1** or **MNP2** were suspended in 1 mL of water in a Falcon® tube. The mixture was stirred with a mechanical shaker for 20 h. Acetone (approx. 10 mL) was added and the suspension was allowed to settle over a 1.2 T NdFeB magnet. The supernatant was removed and the nanoparticles were washed twice with acetone with 10 min shaking for each washing. The joint organic phase was condensed under vacuum. In the case of recycling experiments, the recovered nanoparticles were dried in vacuo and reused immediately by adding again the reactants and water.

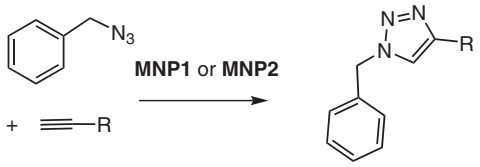
3. Results and discussion

The corresponding imidazolinium salts **L1**·HCl and **L2**·HCl were obtained by a straightforward synthetic sequence at the gram scale previously reported for other similar compounds [19]. Dissymmetric oxalamides were obtained by the reaction of easily prepared iodinated anilines with a monoamide derivative of oxalyl chloride. After reduction of the amide groups, an Ullmann-type reaction was performed to introduce an azide group. The imidazolinium salts were obtained by a cyclization reaction with triethyl orthoformate. Synthetic details are given in the Supporting Information.

Finally, the copper(I)–NHC complexes were obtained by the metalation of the imidazolinium salts with aqueous ammonia as basic and complexing medium and copper(I) chloride [24]. The compounds **C1** and **C2** were characterized spectroscopically to ensure their identity and purity. The neutral heteroleptic nature of the complexes NHC-Cu-Cl was verified by measuring their conductivity in DMSO solution (see ESI for data) and in the case of **C1** by its ^{13}C NMR chemical shift of the carbenic carbon which is very similar to the reported value for CuCl(SIMes) (202.7 *vs.* 202.8 ppm) and thus is diagnostic of the lepticity of the complex [25]. However, as described in a previous paper by Roland *et al.* for silver complexes [26] there may be an equilibration in solution in coordinating solvents for complex **C1**, which results in a concentration-dependent behavior and in the observation of a minor species in the ^{1}H NMR spectrum of **C1**, likely a homoleptic [Cu(**L1**)$_2$](CuCl$_2$) species, which shares the elemental composition of **C1**.

Magnetic nanoparticles functionalized with alkyne groups were prepared using a 3-step sequence described by Gun'ko without any modification: preparation of Fe_3O_4 cores, coating with aminopropyltriethoxysilane and coupling with propiolic acid promoted by EDC.[23] The magnetic nanoparticles were subjected to an auto-click reaction with either of copper(I) complexes (**C1** or **C2**) [19]. The reaction was conducted overnight at 50 °C under ultrasonic irradiation. After the functionalization, a mass similar to the one of the starting nanoparticles was recovered by magnetic decantation followed by several washes.

TEM images of a batch of functionalized nanoparticles with complex **C1** (**MNP1**) show that the mean radius of the nanoparticles is about 20 nm as reported by Gun'ko and that the functionalization reaction did not alter the nanoparticle appearance (ESI). ICP-AES analysis was performed on the nanoparticles after an acidic treatment to uncomplex the copper(I) ions. This analysis shows that the copper loading on **MNP1** is



Scheme 2. Test of the catalytic potential of **MNP1** and **MNP2** in a CuAAC reaction.

about 2.2 mass-%, while **MNP2** displays an 8-times lesser loading (while a blank experiment allows to verify that alkyne-bearing magnetic nanoparticles prior to the auto-click reaction do not contain any detectable copper amounts). The metal loading of **MNP1** is very similar (only 8% difference) to the figure reported by Diez-Gonzalez *et al.* for copper-NHC MNPs for which the copper was introduced on NHC ligand precursors previously grafted onto the nanoparticles [13], hinting to an efficient auto-click reaction in the case of **MNP1**.

Then, we decided to test the catalytic potential of **MNP1** and **MNP2**. To this end, we selected the CuAAC reaction with benzyl azide and phenylacetylene (Scheme 2, R = Ph).

The first tests (Table 1, entries 1 and 2) show that **MNP1** is able to catalyze the reaction in heterogenous aqueous conditions (dispersion of an immiscible organic phase in an aqueous medium) with 20 mg catalytic material for 1 mmol of each substrate, while **MNP2** resulted in very limited conversions. On the other hand, a classical water/*tert*-butanol solvent mixture able to dissolve the reactants did not afford detectable product. This highlights that our nanocatalyst are usable efficiently in *on-water* conditions as was pointed out for other copper-NHC complexes [27]. We tentatively ascribe this reduced reactivity of **MNP2** to reduced copper loading and to reduced reactivity of the copper(I) center

With **MNP1** first substrate scope experiment shows that the azide-alkyne cycloaddition reaction may be conducted with aromatic or other activated alkynes in aqueous dispersion (entries 10–12) and that the products may be obtained in high purity after magnetic decantation and washing (see NMR spectra in the supporting information). Non activated oct-1-yne (entry 13) resulted in only trace amount of the product. Hydrophilic alkynes (entries 14,15) resulted in limited conversions.

Interestingly we have shown that **MNP1** catalysts may be recycled a limited number of times, which corroborates a covalent grafting of the complex. Moreover, as the magnetic nanoparticles are compatible with the metalation reactions in aqueous ammonia used for the complex synthesis,[24] we performed a "reloading" experiment with **MNP1** previously used for 4 catalytic runs (benzyl azide + phenylacetylene). We were able to show that a significant catalytic activity was restored (although not quite as good as pristine **MNP1**) which again correlates with a covalently linked complex, or - after decomplexation during multiple catalytic runs - NHC precursor. Concurrently, if alkyne tagged NHC nanoparticles were subjected to "ammonia metalation conditions" and isolated no catalytic activity was observed suggesting that the catalytic activity belongs to intact heterogenized NHC complexes *or* from Cu^{+} ions leached from the same grafted complexes [28].

To verify the assumption of lesser activity of **C2** which results in lower copper loading and likely in reduced catalytic activity of **MNP2** we performed an auto-click reaction in homogenous conditions as described in a previous paper [19]. Even though it is not feasible to reproduce conditions identical to the MNP functionalization experiments (large excess of copper-NHC complex in comparison to the alkyne counterpart), our results indicate **C1** displays a higher reactivity than **C2** towards an alkyne (propargyl alcohol in our model experiments) albeit the reaction results in the formation of multiple minor compounds (most likely products of ligand rearrangement around the metal center, details are given in the supporting information). Indeed, this observation is compatible with either (or both) hypotheses explaining a reduced catalytic efficiency of **MNP2** as compared to **MNP1**.

Table 1
Outcome of catalytic reactions with **MNP1** or **MNP2.**

Entry	Catalyst	Alkyne	Remarks/ deviation from standard conditions[a]	Yield
1	**MNP1**[b]	Phenylacetylene		93%
2	**MNP2**[c]	Phenylacetylene		22%
3	**MNP1**	Phenylacetylene	0.5 mL H_2O	81%
4	**MNP2**	Phenylacetylene	0.5 mL H_2O	10%
5	**MNP1**	Phenylacetylene	H_2O/^{t}BuOH *v/v* 1:1	–
6	**MNP1**	Phenylacetylene	Catalyst recycling #1	81%
7	**MNP1**	Phenylacetylene	Catalyst recycling #2	37%
8	**MNP1**	Phenylacetylene	Catalyst recycling #3	16%
9	**MNP1**	Phenylacetylene	Catalyst recycling #3 + copper reloading[d]	75%
10	**MNP1**	2-Hydroxymethylphenylacetylene		97%
11	**MNP1**	4-Methoxyphenylacetylene		98%
12	**MNP1**	Methyl propiolate		quant.
13	**MNP1**	Oct-1-yne		trace
14	**MNP1**	4-Ethynylaniline		30%
15	**MNP1**	*N*-Acetylpropargylamine		15%

[a] Standard conditions: 20 mg nanoparticles, 1 mL H_2O, 1 mmol of each substrate. Azide: benzyl azide. Reaction duration: 20 h, RT.
[b] Copper loading: 0.705 mol-%.
[c] Copper loading: 0.088 mol-%.
[d] see ESI.

4. Conclusion

In conclusion, although the catalytic potential of **MNP1** for the CuAAC reaction remains modest in comparison to other copper-loaded MNPs, this communication provides a first proof of concept of an original and simple strategy to heterogenize organometallic complexes. These results could inspire further research on the optimization of the auto-click reaction for nanoparticle functionalization. Moreover, avenues might be opened with other metals, provided that transmetalation from copper is feasible on heterogenized systems similar to **MNP1**.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ica.2021.120312.

References

[1] M.N. Hopkinson, C. Richter, M. Schedler, F. Glorius, Nature 510 (2014) 485–496.

[2] S. Diez-Gonzalez, N-heterocyclic Carbenes: from laboratory curiosities to Efficient Synthetic Tools, Royal Society of Chemistry, 2011.
[3] W.L. Wang, L.F. Cui, P. Sun, L.J. Shi, C.T. Yue, F.W. Li, Chem. Rev. 118 (2018) 9843–9929.
[4] R. Zhong, A.C. Lindhorst, F.J. Groche, F.E. Kuhn, Chem. Rev. 117 (2017) 1970–2058.
[5] V. Kandathil, B.D. Fahlman, B.S. Sasidhar, S.A. Patil, New J. Chem. 41 (2017) 9531–9545.
[6] A. Salamatmanesh, M.K. Miraki, E. Yazdani, A. Heydari, Catal. Lett. 148 (2018) 3257–3268.
[7] A. Taber, J.B. Kirn, J.Y. Jung, W.S. Ahn, M.J. Jin, Synlett (2009) 2477–2482.
[8] A.R. Hajipour, N.S. Tadayoni, Z. Khorsandi, Appl. Organomet. Chem. 30 (2016) 590–595.
[9] K. Vishal, B.D. Fahlman, B.S. Sasidhar, S.A. Patil, Catal. Lett. 147 (2017) 900–918.
[10] R. Fareghi-Alamdari, M.S. Saeedi, F. Panahi, Appl. Organomet. Chem. 31 (2017).
[11] F. Rafiee, N. Mehdizadeh, Catal. Lett. 148 (2018) 1345–1354.
[12] H.J. Yoon, J.W. Choi, H. Kang, T. Kang, S.M. Lee, B.H. Jun, Y.S. Lee, Synlett (2010) 2518–2522.
[13] J.M. Collinson, J. Wilton-Ely, S. Diez-Gonzalez, Chem. Commun. 49 (2013) 11358–11360.
[14] I. Misztalewska-Turkowicz, K.H. Markiewicz, M. Michalak, A.Z. Wilczewska, Journal of Catalysis 362 (2018) 46–54.
[15] (a) See recent reviews E. Haldon, M.C. Nicasio, P.J. Perez, Org. Biomol. Chem. 13 (2015) 9528–9550;
(b) S. Neumann, M. Biewend, S. Rana, W.H. Binder, Macromol. Rapid Commun. 41 (2020), https://doi.org/10.1002/marc.201900359;
(c) K. Bozorov, J.Y. Zhao, H.A. Aisa, Bioorg. Med. Chem. 27 (2019) 3511–3531;
(d) G. Yi, J. Son, J. Yoo, C. Park, H. Koo, Biomater. Res. 22 (2018) 13;
(e) L. Li, Z.Y. Zhang, Molecules 21 (2016) 1393. A. Mandoli, Molecules, 21 (2016), 1174;
(f) V.K. Tiwari, B.B. Mishra, K.B. Mishra, N. Mishra, A.S. Singh, X. Chen, Chem. Rev. 116 (2016) 3086–3240.
[16] F. Lazreg, F. Nahra, C.S.J. Cazin, Coord. Chem. Rev. 293 (2015) 48–79.
[17] F. Nahra, A. Gómez-Herrera, C.S.J. Cazin, Dalton Trans. 46 (2017) 628–631.
[18] C. Gibard, D. Avignant, F. Cisnetti, A. Gautier, Organometallics 31 (2012) 7902–7908.
[19] H. Ibrahim, C. Gibard, C. Hesling, R. Guillot, L. Morel, A. Gautier, F. Cisnetti, Dalton Trans. 43 (2014) 6981–6989.
[20] W. Wang, L. Zhao, H. Lv, G. Zhang, C. Xia, F.E. Hahn, F. Li, Angew. Chem., Int. Ed. 55 (2016) 7665–7670.
[21] V.V. Rostovtsev, L.G. Green, V.V. Fokin, K.B. Sharpless, Angew. Chem., Int. Ed. 41 (2002) 2596–2599.
[22] S. Chassaing, V. Beneteau, P. Pale, Catal. Sci. Technol. 6 (2016) 923–957.
[23] S.A. McCarthy, G.-L. Davies, Y.K. Gun'ko, Nat. Protoc. 7 (2012) 1677–1693.
[24] C. Gibard, H. Ibrahim, A. Gautier, F. Cisnetti, Organometallics 32 (2013) 4279–4283.
[25] D. Tapu, D.A. Dixon, C. Roe, Chem. Rev. 109 (2009) 3385–3407.
[26] E. Caytan, S. Roland, Organometallics 33 (2014) 2115–2118.
[27] S. Diez-Gonzalez, S.P. Nolan, Angew. Chem., Int. Ed. 47 (2008) 8881–8884.
[28] This issue may be solved by monitoring the copper leaching after each catalytic run.