PAPER

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Formation of C–C, C–S and C–N bonds catalysed by supported copper nanoparticles†

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Transition-metal catalysed cross-coupling reactions are still dominated by palladium chemistry. Within the recent past, copper has gained ground against palladium by virtue of its cheaper price and equivalent function in certain reactions. Four catalysts consisting of copper nanoparticles on zeolite, titania, montmorillonite and activated carbon have been tested in three palladium- and ligand-free cross-coupling reactions to form carbon–carbon, carbon–sulfur and carbon–nitrogen bonds. CuNPs/zeolite has been found to be the best one in the Sonogashira reaction of aryl iodides and arylacetylenes, as well as in the coupling of aryl halides with aryl and alkyl thiols, being reusable in both cases. However, the arylation of nitrogen-containing heterocycles (imidazole, pyrazole, benzimidazole and indole) has been better accomplished with CuNPs/titania, albeit CuNPs/activated carbon showed better recycling properties. The catalytic activity of the nanostructured catalysts has been compared with that of twelve commercial copper catalysts, with the former outperforming the latter in the three types of reactions studied.

Introduction

The copper-catalysed formation of carbon–carbon and carbon–heteroatom bonds is not only a simple renaissance of Ullmann's chemistry; it is a new area of transition-metal catalysed reactions where copper sometimes competes with palladium and often reveals quite different behaviour.[1] There are many Cu(ɪ) and Cu(ɪɪ) derivatives, such as salts, oxides, or complexes with ligands which are widely used in catalysis. Even though many of these catalytic systems helped to overcome some of the main drawbacks of traditional copper-promoted procedures, the homogeneous nature of this catalysis hampers the recovery and reuse of these catalysts and their practical applicability,[2] mainly in the synthesis of drug molecules,[3] which must be free of any residual metal. Consequently, heterogeneous copper catalysis has attracted a great deal of attention in recent years. There are many examples in the literature about the utility of heterogeneous copper-based catalysts in cross-coupling reactions, most of them based on copper complexes with functionalised ligands immobilised on different supports.[4] Still, these catalytic systems require

the synthesis of specialised ligands, immobilisation and copper complex formation steps that, often, may catalyse a narrow scope of reactions. In this sense, catalytic systems which rely on Cu nanoparticles (CuNPs) may be good alternatives to immobilised complexes because of their high surface-to-volume ratio, which provides them with higher reactivity and selectivity when compared with bulk catalysts.[5] Although it is difficult to separate nanoparticles using standard methods due to their nanometric size,[6a] immobilisation on inorganic supports not only favours their stabilisation and dispersion but separation from the reaction medium.[6b–f]

Immobilised copper nanoparticles obtained by various methods and on different supports have been demonstrated to be versatile and reusable catalysts for a wide range of reactions, including cross-coupling reactions forming carbon–carbon and carbon–heteroatom bonds (C–N, C–O, C–S, C–P),[4,7] oxidative coupling reactions,[8] as well as multicomponent reactions.[9]

In this work, we set out a broad synthetic application of some copper-based nanocatalysts supported on four different materials: a carbonaceous material (activated carbon),[10] a ceramic metal oxide (nanosized titania),[11] a clay mineral (montmorillonite-K10)[12] and a microporous zeolite (sodium Y zeolite).[13] In particular, we have already demonstrated the great versatility of activated carbon[14] and titania[15] as supports for metal nanoparticles in catalytic organic reactions. Herein, the support-dependent catalytic behaviour has been evaluated in the Sonogashira–Hagihara reaction and in the coupling of aryl halides with thiols and azoles. To the best of our

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† Electronic supplementary information (ESI) available: Catalyst characterisation, experimental procedures, spectroscopic data and NMR spectra of the new compounds. See DOI: 10.1039/c7cy01343d

knowledge, such a comparative study involving four supports of different nature has never been reported for these type of reactions.

Results and discussion

Catalyst preparation and characterisation

The CuNP-based catalysts were prepared following the arene-catalysed[16] chemical reduction of metal salts, as follows;[9b] anhydrous $CuCl_2$ was rapidly reduced with lithium metal and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB) in THF at room temperature, followed by the addition of the support. The resulting mixture was filtered, washed and dried.[9b]

The full characterisation of copper nanoparticles on activated carbon (CuNPs/C)[9b] and copper nanoparticles on zeolite Y (CuNPs/ZY)[8b] was already reported in the literature (see also the ESI†). The copper nanoparticles on titania (CuNPs/TiO_2) and copper nanoparticles on montmorillonite (CuNPs/MK-10)[12b] were characterised by means of transmission electron microscopy (TEM), energy-dispersive X-ray spectroscopy (EDX) and X-ray photoelectron spectroscopy (XPS) (see the ESI†). In general, all the catalysts unveiled the presence of well dispersed spherical nanoparticles on the supports, with average sizes in the range of 1–6 nm. Analysis by XPS revealed that the surface of the CuNPs in all the catalysts is oxidised and consists of both Cu(I) and Cu(II) oxides for CuNPs/C and CuNPs/ZY, mainly Cu(I) oxide for Cu/TiO_2 and Cu(II) oxide for CuNPs/MK-10. The following copper loadings and BET areas were determined using inductively coupled plasma optical emission spectroscopy (ICP-OES) and adsorption isotherms, respectively, for the different catalysts: CuNPs/C (3.5 wt%, 1224 $m^2\ g^{-1}$), CuNPs/TiO_2 (1.9 wt%, 119 $m^2\ g^{-1}$), CuNPs/ZY (3.0 wt%, 621 $m^2\ g^{-1}$) and CuNPs/MK-10 (1.7 wt%, 89 $m^2\ g^{-1}$).

The Sonogashira–Hagihara reaction

The Sonogashira–Hagihara reaction can be considered to be one of the most widely practiced strategies to synthesise alkyl and aryl acetylenes as well as conjugated enynes. In this scenario, palladium has always occupied a leading position as the catalytic metal.[17] Latterly, copper has emerged as a competitive cheaper alternative to palladium, providing in many cases comparable results with simple catalytic systems.[18]

In order to investigate the effect of the nature of the support in the Cu-catalysed Sonogashira coupling, 4-iodoanisole (1a) and phenylacetylene (2a) were chosen as the model substrates. A preliminary screening which considered the catalyst loading, base, solvent and temperature as the variables allowed us to conclude that 5 mol% copper loading and K_2CO_3 as the base in DMF at 120 °C were appropriate conditions for comparative purposes of all the catalysts. As expected, the catalytic activity of the nanoparticles was found to depend on the nature of the support with significant differences and the following decreasing order of activity: CuNPs/ZY > CuNPs/C > CuNPs/MK-10 > CuNPs/TiO_2

(Fig. 1). The higher activity of CuNPs/ZY and CuNPs/C might be, tentatively, correlated with the larger surface area of these supports and the presence of both Cu(I) and Cu(II) in the catalysts.

The most active catalyst (CuNPs/ZY) was deployed in the coupling reaction of phenylacetylene with different aryl halides at a *ca.* 4 mol% loading [determined from the Cu content (3.0 wt%) and the Cu_2O/CuO area from XPS (*ca.* 1:1)] (Table 1).

All reaction products were formed in a selective manner with almost quantitative yields from aryl iodides substituted either with electron-withdrawing or electron-donating groups (3aa–3ea). As expected, electron-poor aryl iodides were shown to be more reactive than those bearing electron-donating groups in the aromatic ring (compare the reaction times of 1a and 1b with those of 1c–1e and 1k). The reaction with haloaryl iodides was highly chemoselective towards the C–I bond (3fa–3ha). Unfortunately, this catalyst was confirmed to be less efficient in the coupling of aryl bromides (1i and 1j) under the standard conditions. The electronic effect on the more reluctant to react substituted arylacetylenes was also analysed *via* reaction with 4-iodobenzonitrile (1c): the lower the electron-rich character of the arylacetylene, the better the yield obtained (3cb–3cd).

The heterogeneous nature of CuNPs/ZY facilitated its recovery by centrifugation and recycling. Indeed, the catalyst showed an excellent performance when reused in four consecutive cycles, in the standard reaction of 4-iodoanisole (1a) and phenylacetylene (2a) (Fig. 2), with no discernible variation in particle size after the fourth cycle (Fig. S5, ESI†). The
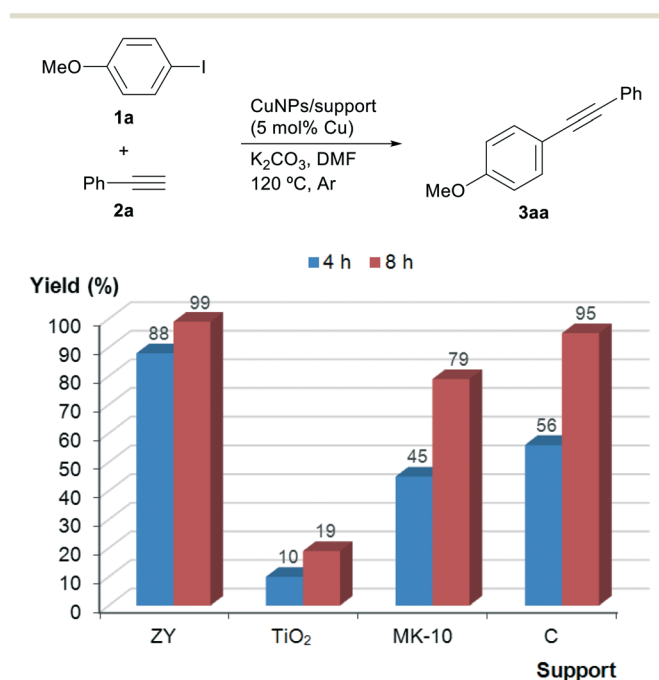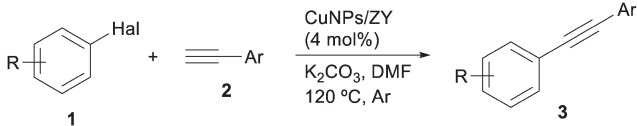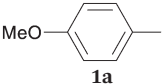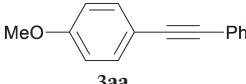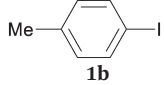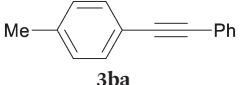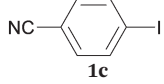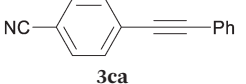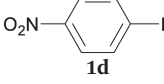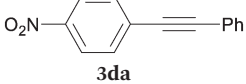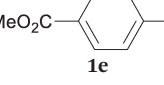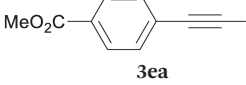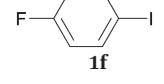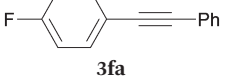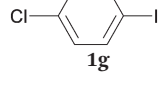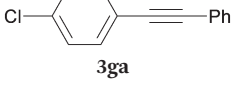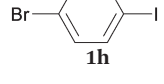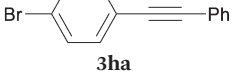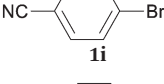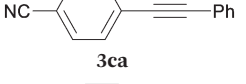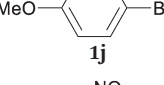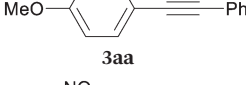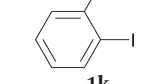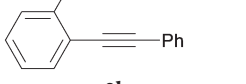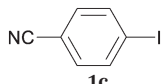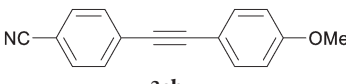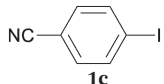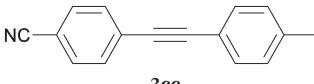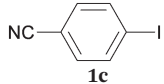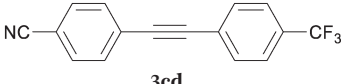

Fig. 1 Sonogashira coupling of **1a** and **2a** catalysed by CuNPs on different supports; **1a** (0.25 mmol), **2a** (1.5 equiv.), catalyst (5 mol% Cu), K_2CO_3 (2 equiv.), DMF (1 mL), 120 °C, 4 or 8 h, Ar; yield of **3aa** determined by ^{1}H NMR.

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Table 1 The coupling of aryl halides and arylacetylenes catalysed by CuNPs/ZY[a]

Aryl halide	t (h)	Product	Yield[b] (%)
MeO—C$_6$H$_4$—I **1a**	8	MeO—C$_6$H$_4$—≡—Ph **3aa**	99
Me—C$_6$H$_4$—I **1b**	8	Me—C$_6$H$_4$—≡—Ph **3ba**	99
NC—C$_6$H$_4$—I **1c**	4	NC—C$_6$H$_4$—≡—Ph **3ca**	98
O$_2$N—C$_6$H$_4$—I **1d**	2	O$_2$N—C$_6$H$_4$—≡—Ph **3da**	95
MeO$_2$C—C$_6$H$_4$—I **1e**	2	MeO$_2$C—C$_6$H$_4$—≡—Ph **3ea**	98
F—C$_6$H$_4$—I **1f**	4	F—C$_6$H$_4$—≡—Ph **3fa**	96
Cl—C$_6$H$_4$—I **1g**	4	Cl—C$_6$H$_4$—≡—Ph **3ga**	98
Br—C$_6$H$_4$—I **1h**	4	Br—C$_6$H$_4$—≡—Ph **3ha**	98
NC—C$_6$H$_4$—Br **1i**	8 / 8[c]	NC—C$_6$H$_4$—≡—Ph **3ca**	25 / 60[cd]
MeO—C$_6$H$_4$—Br **1j**	8	MeO—C$_6$H$_4$—≡—Ph **3aa**	0
(2-NO$_2$)C$_6$H$_4$—I **1k**	2	(2-NO$_2$)C$_6$H$_4$—≡—Ph **3ka**	99
NC—C$_6$H$_4$—I **1c**	24[c]	NC—C$_6$H$_4$—≡—C$_6$H$_4$—OMe **3cb**	40[d]
NC—C$_6$H$_4$—I **1c**	24[c]	NC—C$_6$H$_4$—≡—C$_6$H$_4$—Me **3cc**	61[d]
NC—C$_6$H$_4$—I **1c**	24[c]	NC—C$_6$H$_4$—≡—C$_6$H$_4$—CF$_3$ **3cd**	90[d]

[a] Aryl halide (**1**, 0.25 mmol), arylacetylene (**2**, 1.5 equiv.), CuNPs/ZY (*ca.* 4 mol%) and K$_2$CO$_3$ (0.5 mmol), DMF (1 mL), 120 °C, Ar. [b] ^{1}H NMR yield. [c] Reaction at 150 °C. [d] Isolated yield.

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Fig. 2 Recycling of CuNPs/ZY in the synthesis of 3aa.

hot filtration test after the first run disclosed a leaching of 0.14% of the original copper content (0.01% Cu after the fourth run), as determined by ICP-MS; this leached copper was found to be catalytically inactive.

By comparing the catalytic activity of CuNPs/ZY with that of other catalysts reported in the literature, we can conclude that its activity and that reported by Rothenberg et al. using copper clusters stabilised by tetra-butylammonium acetate (5 mol% Cu, DMF, 110 °C, 24 h) are alike,[19a] e.g., similar reactivity towards various aryl halides. Commercial nano-CuO[19b] manifested lower activity than CuNPs/ZY, given the higher catalyst loading and temperature required for the coupling of aryl iodides (10 mol%, DMSO, 160 °C, 12 h). Neither of the two aforementioned catalysts were reutilised. CuNPs/ZY was not active in the reaction of aryl chlorides with acetylenes, in contrast with Cu(0)NPs/Al$_2$O$_3$ which could catalyse this reaction at room temperature.[7a] The absence of an oxide film on the copper surface seems to be crucial for this enhanced reactivity. Indeed, CuO/Al$_2$O$_3$ not only exhibited relatively lower activity but also was evinced to be non-recyclable, with a copper loss of 63% after the first cycle.[19c] Most importantly, CuNPs/ZY is a clear alternative to PdNPs stabilised by a tris-imidazolium salt[20a] and PdNPs/DNA,[20b] which were previously described by us, though the latter was far more active in the reaction with aliphatic alkynes under milder conditions.

We believe that every laboratory-made catalyst should be more efficient than commercial catalysts used for the same purpose in order to justify the time, materials and human resources employed during its preparation. With this principle in mind, we compared the catalytic activity of CuNPs/ZY with that of a wide variety of commercial copper sources in the coupling reaction of 4-iodoanisole (1a) and phenylacetylene (2a) (Table 2). We were delighted to demonstrate that our catalyst was distinctly superior to the commercial catalysts tested. Only CuOTf and Cu(OTf)$_2$, the most expensive substances in Table 2, furnished the coupling product in moderate conversion albeit with the concomitant formation of substantial amounts of the alkyne homocoupling product (1,4-diphenylbuta-1,3-diyne).[21] It is worthwhile mentioning that in the case of our Sonogashira reactions the diyne by-product, if present, was formed in negligible amounts.

Table 2 Comparison of CuNPs/ZY with commercial copper catalysts in the Sonogashira reaction[a]

Entry	Catalyst	Conversion[b] (%)
1	Cu(0)	0
2	Cu$_2$O	8
3	CuO	0
4	CuCl	5
5	CuCl$_2$	8
6	CuBr	0
7	CuI	4
8	CuOAc	9
9	Cu(OAc)$_2$	7
10	CuOTf	50[c]
11	Cu(OTf)$_2$	67[c]
12	CuBr·SMe$_2$	4
13	CuNPs/ZY	99

[a] 1a (0.25 mmol), 2a (1.5 equiv.), Cu catalyst (4.0 mol%) and K$_2$CO$_3$ (0.5 mmol), DMF (1 mL), 120 °C, Ar, 8 h. [b] Conversion into 3aa determined by GLC based on 1a. [c] The alkyne homocoupling side product 1,4-diphenylbuta-1,3-diyne and 3aa were obtained in a ca. 1:2 ratio.

Thiol arylation

Owing to the paramount importance of thioethers in diverse disciplines, the transition-metal catalysed formation of C–S bonds has attracted a great deal of attention lately.[5c,22] We also decided to explore the capability of the supported copper nanoparticles to catalyse the thiophenol arylation; 4-iodobenzonitrile (1c) and thiophenol (4a) were first studied as model substrates. We were pleased to find that, irrespective of the catalyst, the reaction afforded the coupling product in almost quantitative yields when carried out in DMF and K$_2$CO$_3$ as the base for 2 h at 120 °C. The presence of air or absence of solvent had a detrimental effect on the conversion. A lower temperature (80 °C) allowed a better comparison of the activities of the catalysts. Even so, all catalysts manifested quite analogous activity at relatively low copper loadings but, again, CuNPs/ZY was the most active, giving the product in 91% yield after 4 h (Fig. 3). The reactivity of the catalysts followed the order CuNPs/ZY > CuNPs/MK-10 > CuNPs/TiO$_2$ ≥ CuNPs/C.

Although 5ca was formed in 94% conversion after 4 h at 100 °C, we decided to conduct the substrate scope at 120 °C in order to maximise the yield using CuNPs/ZY at a ca. 0.7 mol% catalyst loading [as determined from the Cu content (3.0 wt%) and the Cu$_2$O/CuO area from XPS (ca. 1:1)] (Table 3). Thiophenol (4a) was successfully coupled with a series of aryl iodides bearing electron-donating and -withdrawing groups as well as halogens. As expected, 4-iodoanisole (1a) reacted more sluggishly giving rise to 5aa in moderate yield, whereas

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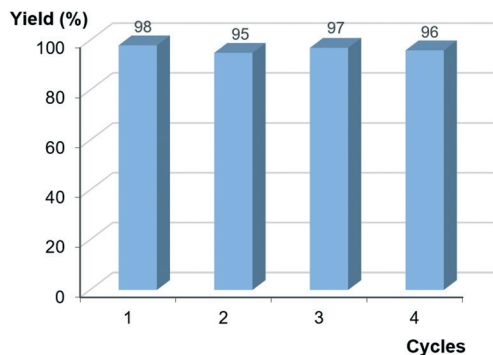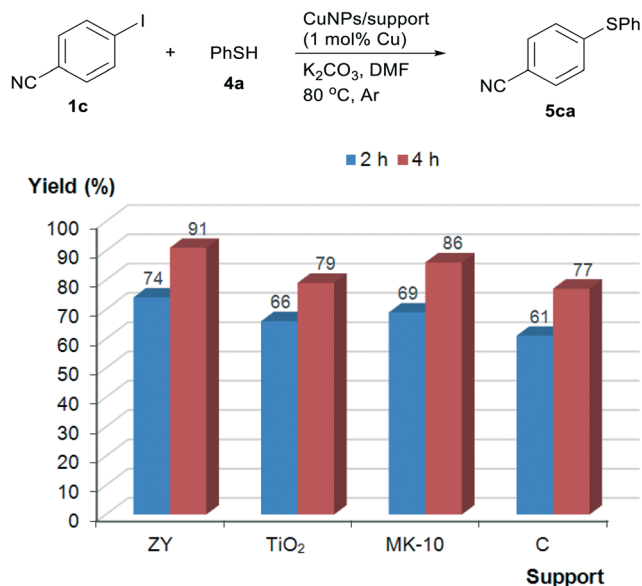**Fig. 3** The cross coupling of 4-iodobenzonitrile (**1c**) and thiophenol (**4a**) catalysed by CuNPs on different supports; **1c** (0.25 mmol), **4a** (1.5 equiv.), catalyst (1 mol% Cu), K$_2$CO$_3$ (2 equiv.), DMF (1 mL), 80 °C, Ar; yield of **5ca** determined by ^{1}H NMR.

excellent yield was recorded for 4-iodotoluene (**1b**). The opposite behaviour was noticed for 4-iodobenzonitrile (**1c**) which furnished the expected diaryl thioether **5ac** in only 2 h. The halogenated iodides **1f** and **1g** reacted chemoselectively towards the activation of the C–I bond, producing the corresponding 4-halogenated thioethers (**5fa** and **5ga**) in near quantitative yields. The presence of electron-donating groups in aryl bromides and chlorides (**1l**–**1j**) made them practically unreactive under these reaction conditions. To our surprise, aryl chlorides bearing electron-withdrawing substituents at the 4- or 2-positions (**1o**–**1r**) participated in this reaction with high efficiency, giving the corresponding coupling products (**5oa**–**5ra**) in high yields after 2 h.

The same procedure at a slightly lower temperature (100 °C) was extended to thiols other than thiophenol, including other aromatic (**4b**–**4d**), heteroaromatic (**4e**–**4f**) and benzylic (**4g**) thiols; 4-iodobenzonitrile (**1c**) was selected as a common partner to furnish the expected thioethers in moderate-to-excellent yields in a relatively short reaction time (4 h) (Table 4). Furthermore, thiolation was feasible for all types of aliphatic thiols, *i.e.*, linear-alkyl (**4h**), branched (**4i**) and cyclic thiols (**4j**); a stronger base (KOH) is, by any means, recommended for upgrading the yields. It is noteworthy that 2,2-dimethyl-ethanethiol (**4i**) reacted quantitatively towards the alkylthio benzonitrile **5ci** under milder conditions (70 °C), whereas the corresponding amide (**5si**) was selectively formed at 120 °C.

Notwithstanding the considerable amount of studies on CuNPs as catalysts for C–S bond formation,[7d,23] they are generally applied to the coupling of thiols with aryl iodides. The coupling with aryl chlorides is limited to a few examples,[7d,23f,g] normally, chloroaromatics bearing electron-withdrawing groups which are coupled with thiophenols.[7,23f]

Table 3 The arylation of thiophenol (**4a**) catalysed by CuNPs/ZY[a]

Aryl halide	t (h)	Product	Yield[b] (%)
1a MeO–C$_6$H$_4$–I	16	**5aa** MeO–C$_6$H$_4$–SPh	60
1b Me–C$_6$H$_4$–I	16	**5ba** Me–C$_6$H$_4$–SPh	97
1c NC–C$_6$H$_4$–I	2	**5ca** NC–C$_6$H$_4$–SPh	99
1f F–C$_6$H$_4$–I	8	**5fa** F–C$_6$H$_4$–SPh	96
1g Cl–C$_6$H$_4$–I	8	**5ga** Cl–C$_6$H$_4$–SPh	96
1l Me–C$_6$H$_4$–Br	16	**5ba** Me–C$_6$H$_4$–SPh	15
1j MeO–C$_6$H$_4$–Br	16	**5aa** MeO–C$_6$H$_4$–SPh	0
1m Me–C$_6$H$_4$–Cl	16	**5ba** Me–C$_6$H$_4$–SPh	0
1n F–C$_6$H$_4$–Cl	16	**5fa** F–C$_6$H$_4$–SPh	0
1o MeO$_2$C–C$_6$H$_4$–Cl	2	**5oa** MeO$_2$C–C$_6$H$_4$–SPh	95
1p (MeCO)–C$_6$H$_4$–Cl	2	**5pa** (MeCO)–C$_6$H$_4$–SPh	99
1q O$_2$N–C$_6$H$_4$–Cl	2	**5qa** O$_2$N–C$_6$H$_4$–SPh	95
1r 2-NO$_2$–C$_6$H$_4$–Cl	2	**5ra** 2-NO$_2$–C$_6$H$_4$–SPh	99

[a] Aryl halide (**1**, 0.25 mmol), thiophenol (**4a**, 1.5 equiv.), CuNPs/ZY (0.7 mol%) and K$_2$CO$_3$ (0.5 mmol) in DMF (1 mL) at 120 °C under Ar. [b] ^{1}H NMR yield.

In other cases, coupling with electron-rich iodides (*e.g.*, 4-iodoanisole) was documented to be troublesome,[7,23a]

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Table 4 The thiolation of 4-iodobenzonitrile (**1c**) catalysed by CuNPs/ZY[a]

Thiol	Product	Yield[b] (%)
4b	**5cb**	98
4c	**5cc**	45
4d	**5cd**	81
4e	**5ce**	52
4f	**5cf**	63
4g	**5cg**	92
4h	**5ch**	80[c]
4i	**5ci**	97[d]
4i	**5si**	60[c]
4j	**5cj**	87[c]

[a] 4-Iodobenzonitrile (**1c**, 0.5 mmol), thiol (**4**, 1.5 equiv.), CuNPs/ZY (0.7 mol%) and K_2CO_3 (1.0 mmol) in DMF (2 mL) at 100 °C for 4 h under Ar, unless otherwise stated. [b] Isolated yield. [c] Reaction using KOH as the base (1.0 mmol) at 120 °C. [d] Reaction using KOH as the base (1.0 mmol) at 70 °C.

whereas very seldom the catalyst was not reusable.[23b] In our case, the nature of CuNPs/ZY differs from that in the literature examples and leads to a catalytic activity between that of Cu(0)/Cu(I)NPs[7d] and CuONPs,[23f,g] albeit the performance with aliphatic thiols is unknown in some cases.[7d,23f]

The recycling studies in the coupling of 4-iodobenzonitrile (1c) and thiophenol (4a) followed a pattern resembling that in the Sonogashira reaction, i.e., the catalyst could be reused in four consecutive runs with no apparent decrease in catalytic activity (Fig. 4). The hot filtration test brought forth 0.12% and 0.02% copper leaching after the first and fourth runs, respectively, which are very close to those observed in the Sonogashira reaction and were also catalytically inert.

Apparently, the nanoparticle–support interaction in CuNPs/ZY is independent of the type of reaction implemented, even when they are so different. As has occurred in the Sonogashira reaction, particle agglomeration was not noticeable after reuse (Fig. S5, ESI†).

Recently, in an interesting research, Ananikov et al. have revealed that unsupported copper oxide-catalysed coupling of aryl halides and thiols takes place through leaching from the surface involving the formation of a copper thiolate.[24] In contrast with our study, the leached copper species were found to be catalytically active.

The catalytic activity of CuNPs/ZY was compared with that of Cu(0) and an array of commercial Cu(I) and Cu(II) catalysts in the reaction of 4-iodobenzonitrile (1c) and thiophenol (4a) (Table 5). The heterogeneous catalysts, Cu(0), Cu₂O and CuO, gave the lowest conversions into the thioether 5ca with the concurrent and abundant formation of the corresponding disulfide (Table 5, entries 1–3). CuCl₂ (our copper source to generate the CuNPs) was the best one within the copper halides, though the conversion was only moderate (Table 5, entries 4–7). However, good-to-high conversions were recorded for Cu(OAc)₂, CuOTf, Cu(OTf)₂ and CuBr·SMe₂ (Table 5, entries 9–12). Nonetheless, CuNPs/ZY can be considered the best choice for this reaction because it led to the highest conversion and the catalyst is recyclable (Table 5, entry 13).

In general, thiol arylation seems to be less dependent on the support, oxidation state and source of Cu (Fig. 3 and

Table 5 Comparison of CuNPs/ZY with commercial copper catalysts in the thiol arylation[a]

$$\text{1c} + \text{PhSH (4a)} \xrightarrow[\substack{K_2CO_3,\ DMF \\ 100\ °C,\ 4\ h,\ Ar}]{\text{Cu catalyst (1 mol\%)}} \text{5ca}$$

Entry	Catalyst	Conversion[b] (%)
1	Cu(0)	25
2	Cu₂O	23
3	CuO	32
4	CuCl	54
5	CuCl₂	64
6	CuBr	38
7	CuI	50
8	CuOAc	63
9	Cu(OAc)₂	91
10	CuOTf	77
11	Cu(OTf)₂	82
12	CuBr·SMe₂	77
13	CuNPs/ZY	94

[a] 1c (0.25 mmol), 4a (1.5 equiv.), Cu catalyst (1 mol%) and K₂CO₃ (0.5 mmol), DMF (1 mL), 100 °C, Ar, 4 h. [b] Conversion into 5ca determined by GLC based on 1c.

Table 5) when put alongside the Sonogashira reaction (Fig. 1 and Table 2).

Arylation of azoles

The formation of C(aryl)–N bonds by the coupling of aryl halides and nitrogen nucleophiles has become one of the most studied copper-catalysed reactions in the last ten years.[2,25] This is not only a valuable tool for the synthesis of heterocycles[25a,c,f] but also a transformation applicable to large-scale production in the pharmaceutical industry.[3b,25d] Although most of the research has been focused on homogeneous catalytic systems,[25e] heterogeneous copper-catalysed processes, including copper nanoparticles,[5a,c] have gained more attention in recent times.

Recently, the preparation and use of CuNPs/MagSilica in the N-arylation of imidazole has been reported.[26] This catalyst successfully catalysed the N-(hetero)arylation of imidazole with (hetero)aryl bromides and iodides but efforts to apply CuNPs/MagSilica to the arylation of other azoles (pyrazole, benzotriazole and indole) were unfruitful. Herein, we have deployed CuNPs on other supports in order to arylate a set of azoles [imidazole (6a), pyrazole (6b), benzimidazole (6c) and indole (6d)] and compare their catalytic activities.

The reactions were implemented using 4-iodobenzonitrile (1c) as a common coupling partner, under equivalent conditions to those for the previous N-arylation of imidazole:[26] catalyst (5 mol% Cu), DMF, K₂CO₃ as the base at 120 °C (instead of 152 °C); the product yields were determined after 16 hours. The reactions proceeded in a selective manner, i.e., the aryl iodide was exclusively converted into the product with no side reactions (Fig. 5). The four catalysts were proven to be active in the N-arylation of all azoles but exhibiting
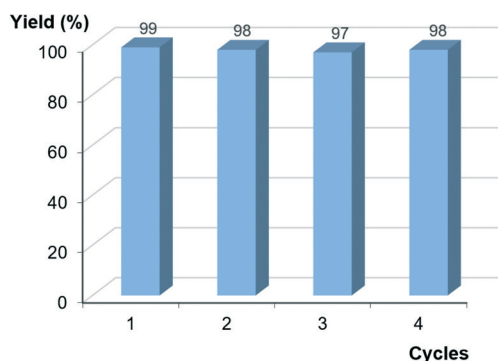

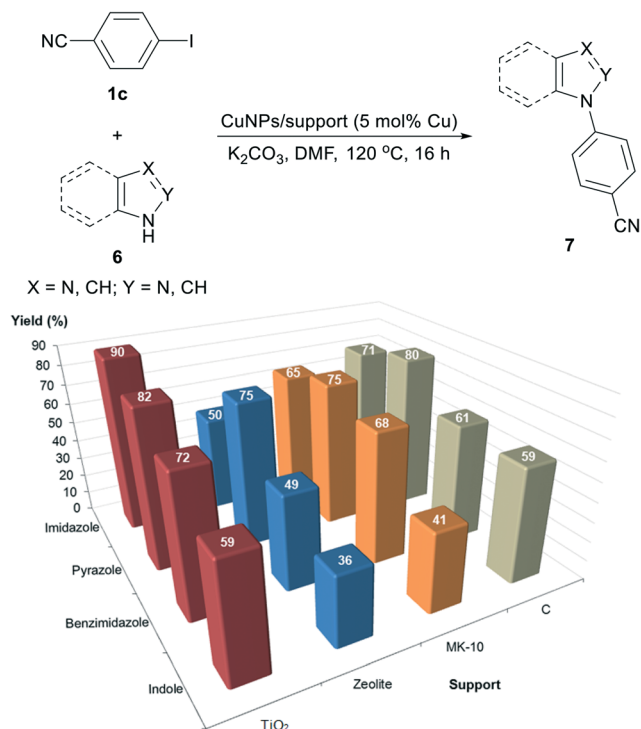**Fig. 4** Recycling of CuNPs/ZY in the synthesis of sulfide 5ca.

Fig. 5 Copper-catalysed coupling of nitrogen-containing heterocycles with 4-iodobenzonitrile (**1c**); **1c** (0.25 mmol), **6** (1.2 equiv.), catalyst (5 mol% Cu) and K_2CO_3 (0.5 mmol), DMF (1 mL), 120 °C, Ar, 16 h; ^{1}H NMR yield.

different activities. In contrast to the copper-catalysed Sonogashira reaction and thiol arylation, in this case, CuNPs/TiO_2 was the most active catalyst for all the studied azoles. Their general catalytic activity follows the sequence Cu/TiO_2 > Cu/C ≈ Cu/MK-10 > Cu/ZY.

Pyrazole (**6b**) was found to be the most reactive azole, producing yields in the range of 75–82%, whereas indole was the least reactive one (36–59%). It is noteworthy that CuNPs/TiO_2 clearly outmatched the other catalysts in the reaction with imidazole (**6a**); taking into account that it is mainly composed of Cu_2O, the real catalyst loading was *ca.* 1.6 mol%. Therefore, the nature of the support seems to exert an influence not only on the activity of CuNPs but also on the reactivity of the azoles. Notably, quantitative yields of *N*-arylated imidazole were reached when employing Cs_2CO_3 as a base instead of K_2CO_3, irrespective of the catalyst utilised (Fig. 6).

The arylation of azoles with aryl halides has been effected with copper nanoparticles in different oxidation states [Cu(0) NPs,[27a–d] CuINPs,[27e] Cu_2ONPs[27f,g] and CuONPs[27h–l]]. Nevertheless, some mechanistic studies consider that Cu(I) species are implicated in the first steps of the catalytic cycles.[28] This could be a reason whereby CuNPs/TiO_2, mainly composed of Cu_2O, displayed better catalytic activity than the other catalysts, which are made of mixtures of Cu_2O and CuO or of CuO.

An attempt to recycle the most active catalyst (CuNPs/TiO_2) in the coupling of imidazole (**6a**) with 4-iodobenzonitrile (**1c**) was unsuccessful; a significant decrease in product yield was observed when the catalyst was reused with K_2CO_3 as the base (Fig. 6). As mentioned before, Cs_2CO_3 usage increased the
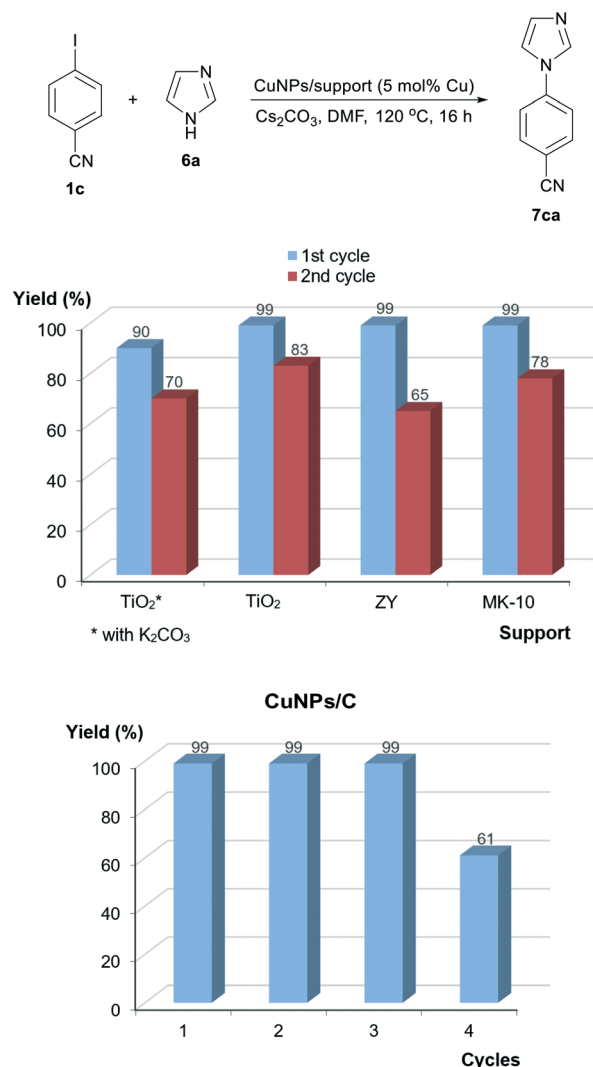
Fig. 6 Recycling of CuNPs/support in the synthesis of **7ca**.

product yield in the first cycle, but a decrease after recycling also took place (from 99 to 83%). A similar trend was observed for ZY and MK-10 (65 and 78% in the second run, respectively); the support seems to influence not only the catalytic activity but also the possibility of recycling. It was gratifying, however, to check that CuNPs/C led to a quantitative yield that was preserved in three cycles; a yield decrease was observed only in the fourth cycle (61%) (Fig. 6).

The leaching issue was assessed for CuNPs/TiO_2 and CuNPs/C in the reaction of 4-iodobenzonitrile (**1c**) and imidazole (**6a**). Using CuNPs/TiO_2 as a catalyst, 44% conversion was noted in the first run after 4 h (with catalyst). The catalyst was then removed by hot filtration after this 4 h period and the reaction heated for a further 12 h (without catalyst), giving a conversion of 47% after this total 16 h period. The copper content in the filtrate was determined to be 0.02 wt% of the original amount. In the case of CuNPs/C, the leaching was also marginal in both the second (0.005 wt%) and fourth cycles (0.05 wt%). The negligible, catalytically inactive leaching detected with CuNPs/TiO_2 reveals a quite strong metal–support

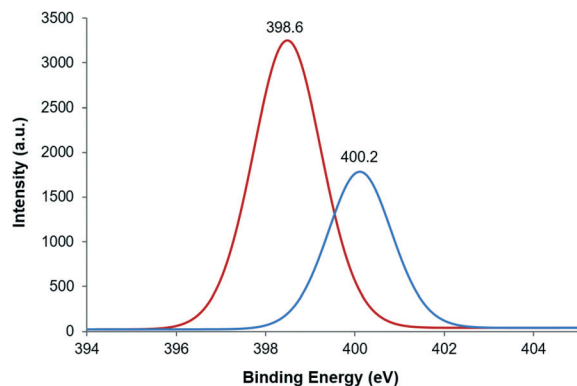**Fig. 7** XPS spectra at the N 1s level of reused CuNPs/TiO$_2$.

interaction in the catalyst, with no notable change in the latter after reuse (Fig. S5 and S6, ESI†). These facts point to a possible poisoning effect as the main reason for partial deactivation and yield depletion upon recycling CuNPs/TiO$_2$. Metal oxides possess surface acid–base properties, which can facilitate the adsorption and accumulation of heteroatom-containing species. Conversely, CuNPs/C, with the less reactive charcoal surface, must interact more weakly with those species, allowing its efficient reuse in several cycles until certain saturation occurs, with the concomitant yield attenuation.

XPS analysis on reused CuNPs/TiO$_2$ at the N 1s level brought into view two peaks at 398.6 and 400.2 eV (Fig. 7). These peaks are consistent with those displayed by fresh CuNPs/TiO$_2$ impregnated with 4-iodobenzonitrile (398.8 and 400.4 eV) (Fig. S7, ESI†) and with that described for imidazole (400.2 eV).[29] This reinforces the hypothesis of the starting materials being strongly adsorbed on the TiO$_2$ surface and their poisoning effect upon reuse.

As in the previous coupling reactions, we also compared the catalytic activity of CuNPs/TiO$_2$ with that of the same commercial copper catalysts as above in the arylation of imidazole (**6a**) with 4-iodobenzonitrile (**1c**) (Table 6). It is worth noting that Cu$_2$O and CuO, which were rather inactive in both the Sonogashira and thiol arylation reactions, led to conversions of around 75% (Table 6, entries 2 and 3); the behaviour of the Cu(ɪ) and Cu(ɪɪ) triflates was akin to that of the Cu oxides (Table 6, entries 10 and 11). Still, once more, the nanostructured catalyst showed the highest performance with a quantitative conversion (Table 6, entry 13).

Conclusions

We have presented herein a comparative survey on the catalytic activity of four catalysts, comprising copper nanoparticles on different supports (zeolite Y, titania, montmorillonite K-10 and activated carbon), in three types of reactions: the Sonogashira reaction, the arylation of thiols and the arylation of azoles. CuNPs/ZY was the most effective catalyst for the Sonogashira reaction (4 mol% catalyst, K$_2$CO$_3$, DMF, 120 °C), being applicable to aryl iodides bearing either electron-donating or -withdrawing groups; aryl bromides reacted more

Table 6 Comparison of CuNPs/ZY with commercial copper catalysts in the arylation of azoles[a]

Entry	Catalyst	Conversion[b] (%)
1	Cu(0)	28
2	Cu$_2$O	74
3	CuO	78
4	CuCl	44
5	CuCl$_2$	46
6	CuBr	18
7	CuI	62
8	CuOAc	25
9	Cu(OAc)$_2$	52
10	CuOTf	78
11	Cu(OTf)$_2$	67
12	CuBr·SMe$_2$	55
13	CuNPs/TiO$_2$	99

[a] **1c** (0.25 mmol), **6a** (1.2 equiv. mmol), catalyst (1.6 mol%) and Cs$_2$CO$_3$ (0.5 mmol), DMF (1 mL), 120 °C, Ar, 16 h. [b] Conversion into **7ca** determined by GLC based on **1c**.

sluggishly. The same catalyst at a lower loading (0.7 mol%) allowed the coupling of thiophenol with aryl iodides of different electronic character but also with electron-poor aryl chlorides in near quantitative yields. Moreover, alkyl thiols were successfully coupled when KOH was used as the base instead of K$_2$CO$_3$. As regards the azole arylation, CuNPs/TiO$_2$ (1.6 mol%) achieved the highest conversion in the coupling of 4-iodobenzonitrile with imidazole, pyrazole, benzimidazole and indole, using K$_2$CO$_3$ as the base. Anyhow, all the catalysts reached quantitative yields when K$_2$CO$_3$ was changed to Cs$_2$CO$_3$ as the base.

This comparative study has been extended to a collection of twelve commercial copper catalysts; only CuOTf and Cu(OTf)$_2$ maintained a moderate-to-good activity in the three reactions examined (50–82% conversion). The rest of the catalysts failed in the Sonogashira reaction (<9% conversion), whereas CuBr·SMe$_2$ and Cu(OAc)$_2$ in the thiol arylation, and Cu$_2$O and CuO in the azole arylation gave comparable results to those attained with the copper(ɪ) and (ɪɪ) triflates. At any rate, in general, the nanoparticulate supported catalysts are markedly superior to the commercial catalysts in terms of catalytic activity and reusability; they can be reused in four (Sonogashira and thiol arylation) and three (azole arylation) cycles with no loss of activity. The negative filtration test and insignificant leaching lend weight to the argument that the catalysis is heterogeneous, taking place at the nanoparticle surface; the possibility of leached Cu from the CuNPs which get into a homogeneous catalytic cycle can, practically, be ruled out. Hence, taking into account that the catalysts are easily prepared, the protocols introduced in this report are an attractive alternative to the

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utilisation of the more expensive palladium catalysts and commercial (non-reusable) copper catalysts.

Experimental

General procedure for the preparation of the catalysts

All the supported copper catalysts handled in this work were prepared by adding the support (titania,[8a] zeolite Y,[8b] activated carbon[14b] or montmorillonite K-10) to a newly prepared suspension of the CuNPs readily generated, in turn, by the chemical reduction of copper(II) chloride with lithium metal and a catalytic amount of 4,4'-di-*tert*-butylbiphenyl (DTBB) as an electron carrier. In a general procedure: anhydrous copper(II) chloride (134 mg, 1 mmol) was added to a suspension of lithium (14 mg, 2 mmol) and DTBB (27 mg, 0.1 mmol) in THF (2 mL) at room temperature under an argon atmosphere. The reaction mixture, which was initially dark blue, rapidly changed to black, indicating that a suspension of copper nanoparticles was formed. This suspension was diluted with THF (18 mL) followed by the addition of the support (1.28 g). The resulting mixture was stirred for 1 h at room temperature, filtered, and the solid was successively washed with water (20 mL), THF (20 mL), and dried under vacuum. The supported catalysts were not subjected to any other treatment prior to use.

General procedure for the cross coupling of aryl iodides (1) with arylacetylenes (2) catalysed by CuNPs/ZY (Table 1)

The aryl halide (1, 0.25 mmol), arylacetylene (2, 0.375 mmol, 1.5 equiv.), CuNPs/ZY (26.7 mg, *ca.* 4 mol%), K$_2$CO$_3$ (69 mg, 0.5 mmol) and DMF (1 mL) were added to a reactor tube. The mixture was warmed to 120 °C under Ar and stirred for the specified time in Table 1. The reaction crude was diluted with EtOAc (3 mL) and filtered through a pad with Celite, followed by extraction of the filtrate with water (3 × 3 mL) to remove the DMF, washing with brine (4 mL) and drying with anhydrous MgSO$_4$. The resulting organic phase was subjected to solvent evaporation under vacuum and to ^{1}H NMR analysis (mesitylene as the internal standard) for products **3aa–3ka** or to purification by column chromatography (silica gel, hexane/EtOAc) for products **3cb–3cd**.

General procedure for the cross coupling of aryl halides (1) with thiophenol (4a) catalysed by CuNPs/ZY (Table 3)

The aryl halide (1, 0.25 mmol), thiophenol (4a, 38 μL, 0.375 mmol, 1.5 equiv.), CuNPs/ZY (5.3 mg, 0.7 mol%), K$_2$CO$_3$ (69 mg, 0.5 mmol) and DMF (1 mL) were added to a reactor tube. The mixture was warmed to 120 °C under Ar and stirred for the specified time in Table 3. The reaction crude was diluted with EtOAc (3 mL) and filtered through a pad with Celite, followed by extraction of the filtrate with water (3 × 3 mL) to remove the DMF, washing with brine (4 mL) and drying with anhydrous MgSO$_4$. The resulting organic phase was subjected to solvent evaporation under vacuum and ^{1}H NMR analysis (mesitylene as the internal standard).

General procedure for the cross coupling of 4-iodobenzonitrile (1c) with thiols (4) catalysed by CuNPs/ZY (Table 4)

4-Iodobenzonitrile (**1c**, 114.5 mg, 0.5 mmol), the thiol (**4**, 0.75 mmol, 1.5 equiv.), CuNPs/ZY (10.6 mg, 0.7 mol%), K$_2$CO$_3$ (138 mg, 1.0 mmol) or KOH (1.0 mmol) and DMF (2 mL) were added to a reactor tube. The mixture was warmed to 70 or 100 °C under Ar and stirred for 4 h. The reaction crude was diluted with EtOAc (6 mL) and filtered through a pad with Celite, followed by extraction of the filtrate with water (3 × 6 mL) to remove the DMF and washing with brine (8 mL). The resulting organic phase was subjected to solvent evaporation under vacuum and purification by column chromatography (silica gel, hexane/EtOAc).

General procedure for the cross coupling of 4-iodobenzonitrile (1c) with azoles (6)

4-Iodobenzonitrile (**1c**, 57.3 mg, 0.25 mmol), the corresponding azole (**6**, 0.3 mmol, 1.2 equiv.), the CuNP catalyst (5 mol% Cu), K$_2$CO$_3$ (69 mg, 0.5 mmol) and DMF (1 mL) were added to a reactor tube. The mixture was warmed to 120 °C under Ar and stirred for 16 h. The reaction crude was diluted with EtOAc (3 mL) and filtered through a pad with Celite, followed by extraction of the filtrate with water (3 × 3 mL) to remove the DMF, washing with brine (4 mL) and drying with anhydrous MgSO$_4$. The resulting organic phase was subjected to solvent evaporation under vacuum and ^{1}H NMR analysis (mesitylene as the internal standard).

Conflicts of interest

There are no conflicts to declare.

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