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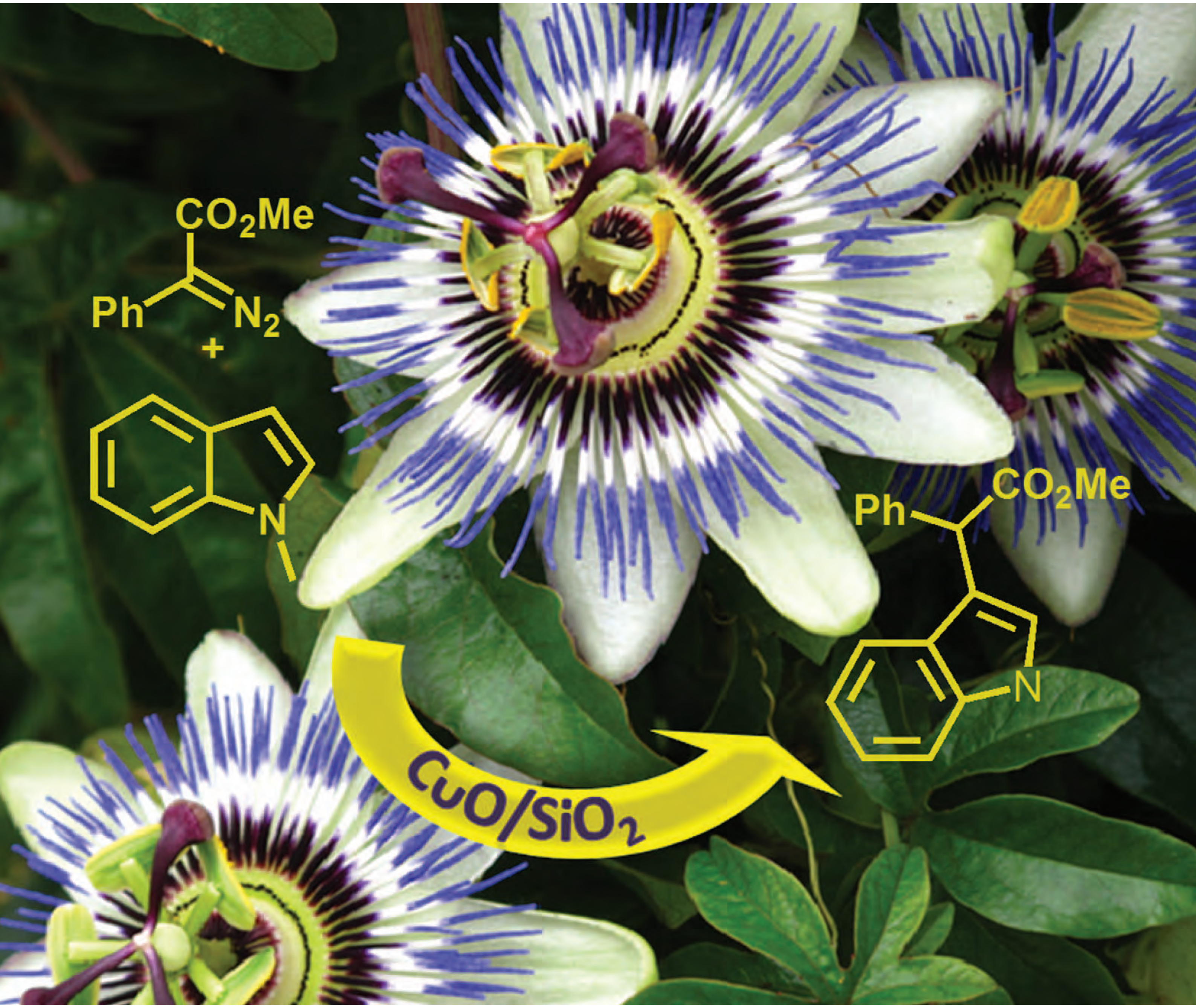

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CuO/SiO$_2$ as a simple, effective and recoverable catalyst for alkylation of indole derivatives with diazo compounds†

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The purely inorganic copper oxide on silica catalyzes the reaction of methyl phenyldiazoacetate with *N*-methyl indole under mild reaction conditions, giving the alkylation (formally a C–H insertion) in position 3, and the catalyst can be recovered and reused at least in 5 consecutive runs with only minor loss in activity. The scope of the reaction includes various diazo compounds and indole or pyrrole derivatives leading to alkylation or cyclopropanation depending on the heterocycle structure. An alternative mechanism, without reduction of Cu(II) to Cu(I), is proposed on the basis of the obtained results.

1 Introduction

The indole structure is one of the most ubiquitous heterocycles in nature. Owing to their presence in many natural bioactive alkaloids,[1–4] the synthesis of indole derivatives became the subject of intensive investigations.[5–7] Among them, the direct functionalization of preformed indoles appears to be a remarkably efficient and versatile route to complex indole derivatives.[8–11] For this purpose, insertion of carbenoids, resulting from the metal catalyzed degradation of diazo compounds,[12–15] represents a powerful and attractive tool whose result depends on both the nature of the indole and the diazo compound.[16] Reaction of indole itself or *N*-alkyl indoles usually leads to C–H insertion with any type of diazo compound and different catalysts, such as rhodium carboxylates,[17–21] copper salts,[22–24] InBr$_3$,[22] and iron complexes.[25] Recently, it was shown that selective insertion in position 2 of indole can be obtained using ruthenium catalysts.[26] In contrast, *N*-acyl indoles are prone to undergo cyclopropanation in either the pyrrole ring[23,27,28] with Cu catalysts or even in the benzene moiety[29] with Rh. In spite of the versatility and the efficiency of this methodology, to the best of our knowledge the only example described with a heterogeneous catalyst is the seminal work of Wenker *et al.* with copper-bronze.[30] Frequently selectivity or even activity of metal catalysts depends on the oxidation state of this metal. In solution redox processes together with a controlled atmosphere are frequently used to adapt the catalyst to the mechanistic requirements of the reaction, but these changes are not so easy with heterogeneous catalysts. Furthermore the use of ambient conditions increases the practical applicability of the catalysts. For these reasons the development of catalysts able to stabilize the required oxidation state of the metal under ambient conditions is an interesting task.

In the course of our study on the preparation of heterogeneous copper catalysts for the C–H insertion into cyclic ethers,[31,32] we described the use of a very simple and purely inorganic CuO$_x$/silica–alumina catalyst for the insertion of phenyldiazoacetate into the C–H bond of THF[33] showing that catalysts that stabilize Cu(I) are more active for this reaction, in agreement with the accepted mechanism. As a continuation of our study, we report herein the extension of the use of this type of catalyst to indole functionalization. Furthermore the results allow us to obtain new mechanistic insights and reinforce the importance of adapting the catalyst even for apparently related reactions. On the other hand the development of cheap, easily obtained and reusable catalysts is necessary to increase the practical application of these reactions.

2 Experimental

Typical conditions for the alkylation of indole derivatives

A solution of indole derivative (0.75 mmol) in DCM (3 mL) was added to a dried powder of CuO/SiO$_2$ (copper content 4% wt,

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† Electronic supplementary information (ESI) available: Experimental methods (catalyst preparation, synthesis of indole derivatives, synthesis of diazo compounds) and identification of all the reaction products. See DOI: 10.1039/c3ob40264a

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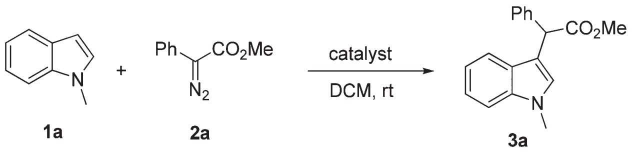
5 mol%). To the resulting suspension was added a solution of diazo compound (0.5 mmol) in DCM (2 mL) in 2 hours with a syringe pump. The reaction mixture was stirred at room temperature for 15 hours. Then, concentration and direct purification with flash chromatography afforded the desired product. Methyl 2-(1-methyl-1*H*-indol-3-yl)-2-phenylacetate (**3a**). Chemical yield: 89%; colorless oil; R_f (Hex–AcOEt 80/20) 0.44; ^{1}H NMR: 7.41–7.47 (m, 3H), 7.19–7.35 (m, 5H), 7.04–7.10 (m, 2H), 5.27 (s, 1H), 3.76 (s, 3H), 3.75 (s, 3H); ^{13}C NMR: 173.6, 138.8, 137.1, 128.7, 128.5, 128.0, 127.3, 127.1, 122.0, 119.4, 119.1, 112.2, 109.5, 52.4, 48.9, 32.9; HRMS (ESI-MS) *m*/*z*: $[M + H]^+$, calcd for $C_{18}H_{18}NO_2^+$, 280.1332, found 280.1328.

3 Results and discussion

3.1 Reaction between *N*-methylindole (1a) and methyl phenyldiazoacetate (2a)

The catalysts were prepared by the chemisorption–hydrolysis method,[34–38] on three different supports, silica gel (surface area: S_A = 300 m^2 g^{-1}), SiO_2–AlO_3 (13% alumina, S_A = 485 m^2 g^{-1}) and TiO_2 (Degussa P-25 80% anatase, 20% rutile, S_A = 50 m^2 g^{-1}). The support is added to a solution of $[Cu(NH_3)_4]^{2+}$ at pH = 9, the copper precursor is hydrolyzed at 273 K, and the solid is filtered, dried, and calcined in air at 673 K. This preparation method exploits the electrostatic interaction taking place well above the point of zero charge of silica and titania between the support surface and the $[Cu(NH_3)_4]^{2+}$ complex solution.[39] This ensures a very high dispersion of the CuO phase on the two supports, particularly on the one having a higher surface area, namely silica.[34,35] In contrast, the number of strong acid sites of silica alumina determined by adsorption calorimetry is close to that determined for an H-Beta zeolite sample.[36] This favours an ionic exchange reaction with the $[Cu(NH_3)_4]^{2+}$ solution that generates isolated $Cu^{\delta+}$ ($1 \leq \delta \leq 2$) species.[37,38] A Cu loading of 4% was used in all cases.

The reaction test was performed with *N*-methylindole **1a** and methyl phenyldiazoacetate **2a** (Scheme 1) in dichloromethane. The results are gathered in Table 1. The diazo compound was added in two hours to minimize the formation of dimerization products (dimethyl 2,3-diphenylmaleate and fumarate). The best catalyst for THF insertion,[33] Cu/SiO_2–AlO_3, affords 75% yield within 15 h (entry 2), similar to that obtained with $Cu(OTf)_2$ (entry 1). However in the case of the homogeneous catalyst an important amount of dimers was detected, in contrast with the lack of these by-products with the heterogeneous catalyst. Interestingly the use of silica as a support improved these results leading to 89% yield in only 4 hours (entry 3). In contrast, titania as the support provides very poor yield (8%, entry 4), although it has some catalytic effect, as shown in the control experiment (entry 10). Finally, a lower amount of catalysts can be used but longer reaction times are required to reach similar yields (79% in 15 h, entry 5). The heterogeneous nature of the catalyst was tested by filtration experiments. As the reaction did not proceed in solution, degradation of the heterogeneous catalyst, leading to catalytically active copper in solution, can be excluded as the catalysis mechanism. Additionally the catalyst exhibited a great hardiness, illustrated by its behaviour upon recovery (Table 1). The yield remains almost the same during 5 cycles (entries 6–9), and the longer reaction time required from cycle 4 is probably due to the unavoidable loss of the catalyst in the filtration process.



Scheme 1 Reaction between *N*-methylindole (**1a**) and methyl phenyldiazoacetate (**2a**).

Table 1 Optimization of reaction conditions[a]

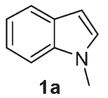
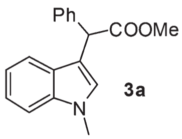
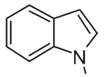
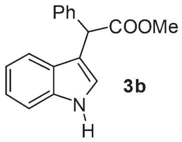
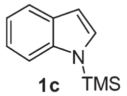
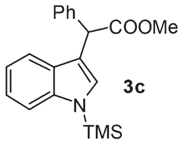
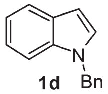
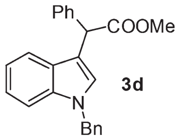
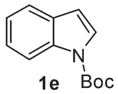
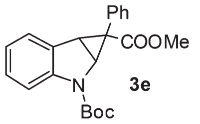
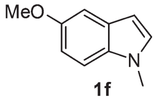
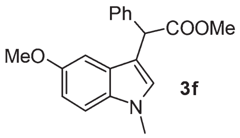
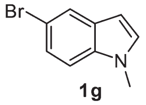
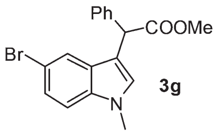
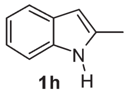
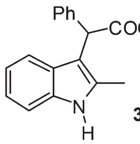
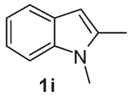
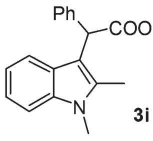
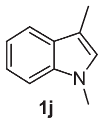
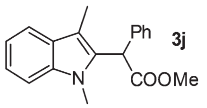
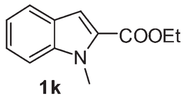
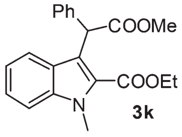
Entry	Catalyst (% mol)	Run	Time (h)	Yield[b] (%)
1	$Cu(OTf)_2$ (5)	1	15	70
2	CuO_x/SiAl (5)	1	15	75
3	CuO/SiO_2 (5)	1	4	89
4	CuO/TiO_2 (5)	1	15	8
5	CuO/SiO_2 (2)	1	15	79
6	CuO/SiO_2 (5)	2	4	84
7		3	4	80
8		4	15	84
9		5	15	92
10	None	1	48	<1

[a] Conditions: Catalyst (2–5% mol) and **1a** (0.75 mmol) in CH_2Cl_2 (3 mL) at rt, addition of **2a** (0.5 mmol in CH_2Cl_2, 2 mL) in 2 h. [b] Determined by GC, eicosane as the internal standard.

3.2 Scope of the reaction: indole structure

Once the optimization of the conditions is accomplished, the scope of the reaction was explored. First of all the structure of the indole substrate was modified (Table 2). Regarding *N*-substitution (entries 1–5), the *N*-unprotected indole **1b** is compatible with this method, and no *N–H* insertion was observed (entry 2).[40] The presence of a bulky substituent such as TMS (**1c**) seems to make the approach of the indole to the surface metal-carbenoid more difficult. Thus, a gentle warming is necessary to reach a moderate yield (61% overall yield), but accompanied by some nitrogen deprotection (14%, entry 3). The reactivity of *N*-benzylindole (**1d**, entry 4) is nearly the same as that of *N*-methylindole. The presence of an electron-withdrawing substituent in *N*-Boc-indole leads to a high yield of the cyclopropanation product **3e**, as a mixture of two diastereomers (1 : 1 ratio), the same chemoselectivity described with Cu-$(OTf)_2$,[23] and in contrast with the double cyclopropanation in the benzenoid ring obtained with $Rh_2(DOSP)_4$.[29] The insertion product was not observed even when the reaction was carried out at 80 °C. Neither the presence of bromo or methoxy substituents in position 5 (entries 6 and 7) nor that of a methyl group in position 2 (entries 8 and 9) had any significant influence on the results, and high yields of the insertion

Table 2 Reactions of methyl phenyldiazoacetate (**2a**) with indole derivatives[a]

Entry	Indole	Temp.	Product	Yield[b] (%)
1	 **1a**	rt	 **3a**	89
2	 **1b**	rt	 **3b**	75
3[c]	 **1c**	50 °C	 **3c**	47 (14)[d]
4	 **1d**	rt	 **3d**	82
5	 **1e**	rt	 **3e**	86
6	 **1f**	rt	 **3f**	78
7	 **1g**	rt	 **3g**	83
8	 **1h**	rt	 **3h**	70
9	 **1i**	rt	 **3i**	90
10[c]	 **1j**	50 °C	 **3j**	41
11[c]	 **1k**	50 °C	 **3k**	50

[a] Conditions: CuO/SiO$_2$ (5% mol) and **1** (0.75 mmol) in CH$_2$Cl$_2$ (3 mL), addition of **2a** (0.5 mmol in CH$_2$Cl$_2$, 2 mL) in 2 h. [b] Isolated yield. [c] Reactions performed in 1,2-dichloroethane. [d] In brackets yield of **3b**.

products were obtained. In contrast, the presence of an electron-withdrawing group in position 2 leads to a drastic drop in reactivity, as described in the case of insertions with diazomalonate,[24] and only a moderate yield at higher temperature can be obtained (entry 11). However, the lower electron density of the indole ring does not promote in this case the cyclopropanation. When position 3 is already substituted, the insertion takes place at position 2, but again with lower reactivity (entry 10).

3.3 Scope of the reaction: diazo compounds

In a second set of experiments, the scope with regard to the diazo compound was studied (Table 3). Modification of the aryl moiety of the donor–acceptor diazo compound[41] with Br or methoxy groups does not bring about significant modification of the yield (entries 1 and 2). Other donor–acceptor diazo compounds undergo side reactions instead of insertion. With *tert*-butyl 2-diazohydrocinnamate (**2d**) only the cinnamates (*Z*–*E* mixture) from β-hydride migration are detected (entry 3).[42,43] In the case of the vinyl diazo compound **2e** an intramolecular 1,5-electrocyclization gives rise to the corresponding pyrazole derivative (entry 4).[44–47] To avoid the cyclization, the unsaturated diazolactone **2f**, with a forced s-*trans* conformation, was considered (entry 5).[48,49] In this case, the yield is lower than usual, and the expected product **4fa** (27% yield) is obtained together with the vinylogous isomer **4fb** (11% yield). This vinylogous reactivity had not been observed in other reactions with this diazolactone.[50] At higher temperature more complex reaction mixtures are obtained, without increasing the yield.

An acceptor diazo compound, such as *tert*-butyl diazoacetate (**2g**), leads to the corresponding insertion product with moderate yield (39%, entry 6) at 50 °C. The reaction performed with the acceptor–acceptor dimethyl diazomalonate (**2h**) needs to be heated at 80 °C to obtain good yield of the insertion product (85%, entry 6).

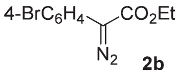
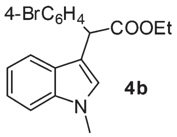
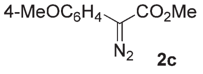
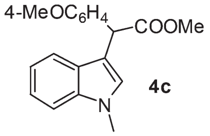
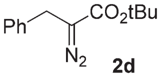
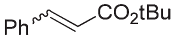
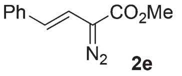
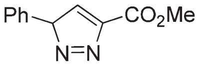
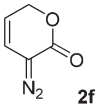
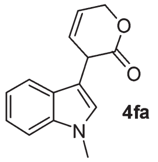
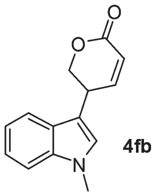
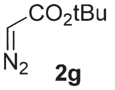
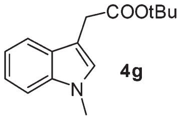
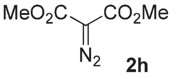
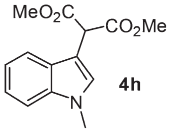
3.4 Reaction with pyrroles

Finally, the reaction of methyl phenyldiazoacetate (**1a**) with pyrrole derivatives (Scheme 2) was tested. With pyrrole itself (**5a**), high conversion of the diazo compound (83%) was obtained to the insertion products, only in position 2 as obtained with other catalysts[26] and diazo compounds,[51–53] and with a significant amount of double insertion product (**7a**). In the case of the *N*-Boc-pyrrole, as expected, instead of C–H insertion cyclopropanation occurs in good yield (90% conversion of phenyldiazoacetate, eqn (2)). In this case, both monocyclopropane **6b** (two rotamers) and dicyclopropane **7b** (one single compound) are obtained. The latter is the only product obtained with Rh under conditions close to the stoichiometric ones,[29] whereas the analogous monocyclopropane can be obtained with Cu catalysts and diazoacetate.[54,55]

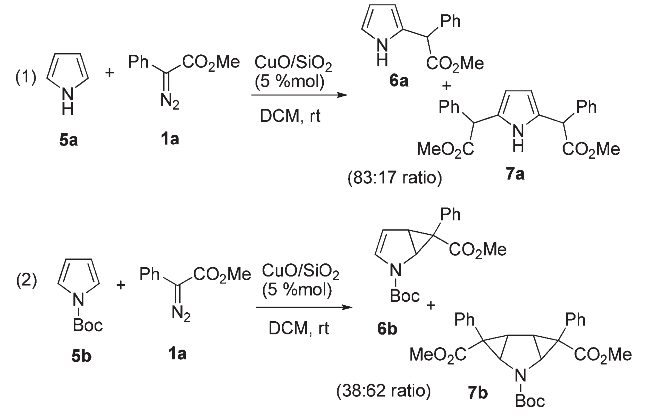
3.5 Reaction mechanism

The mechanism of this kind of reaction is still a matter of debate. It has been proposed that insertion takes place

Table 3 Reactions of different diazo compounds with *N*-methylindole (**1a**)[a]

Entry	Diazo compound	Temp.	Product	Yield[b] (%)
1	 **2b**	rt	 **4b**	79
2	 **2c**	rt	 **4c**	85
3	 **2d**	rt	 E/Z = 1:1	—
4	 **2e**	rt		—
5	 **2f**	rt	 **4fa**  **4fb**	27
6[c]	 **2g**	50 °C	 **4g**	11
7[c]	 **2h**	80 °C	 **4h**	39

[a] Conditions: CuO/SiO_2 (5% mol) and **1a** (0.75 mmol) in CH_2Cl_2 (3 mL), addition of **2** (0.5 mmol in CH_2Cl_2, 2 mL) in 2 h. [b] Isolated yield. [c] Reactions performed in 1,2-dichloroethane.

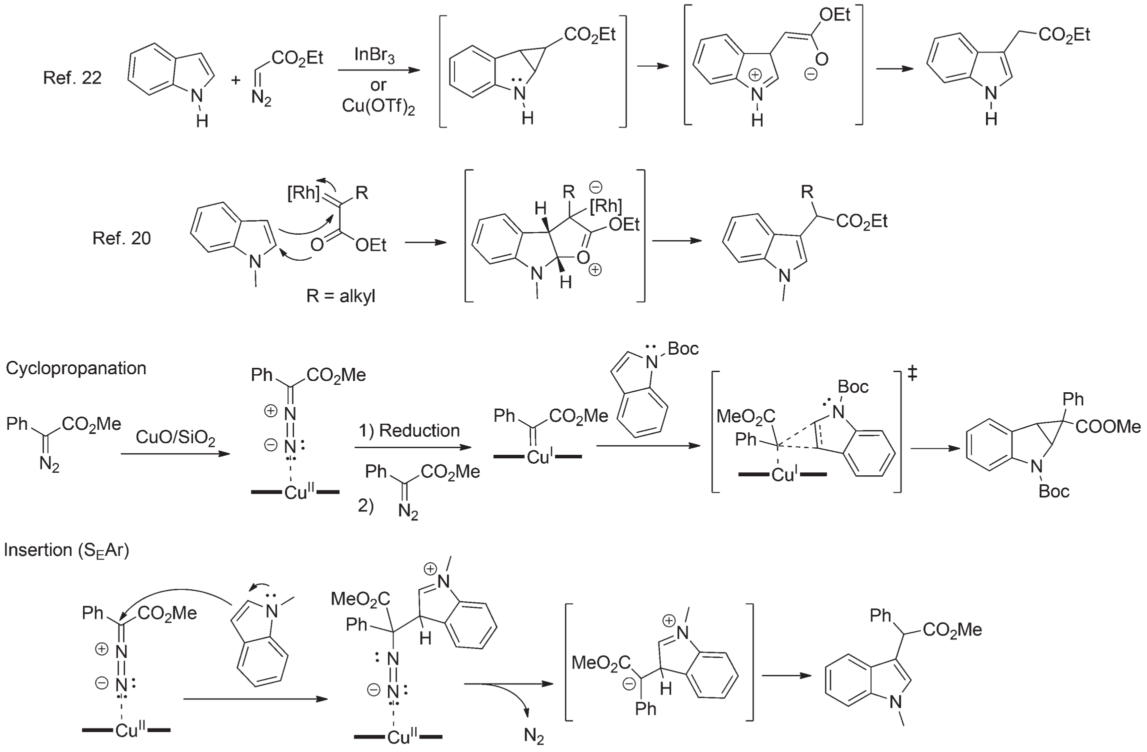


Scheme 2 Reactions of pyrroles with methyl phenyldiazoacetate (**1a**) catalyzed by CuO/silica.

through the opening of a transient cyclopropane in the case of *N*-alkyl and unprotected indoles[18] and pyrroles[22] (Scheme 3). This opening would not take place in the case of *N*-acylindoles and cyclopropane would be obtained as the main (or only) product. Other authors have proposed the formation of an ylide by attack of the indole on Rh-carbene intermediates.[17,56] This mechanism has been supported by DFT calculations for reactions with alkyldiazoacetates[20] (Scheme 3), and it has also been proposed for the case of Cu catalysts.[18] However, Cu(I) has been recognized as the truly catalytic species in reactions, such as cyclopropanation,[57] proceeding through Cu-carbene intermediates, and those Cu(I)-carbene intermediates can be obtained from Cu(II) precursors by *in situ* reduction with the diazo compound.[58,59] This kind of reduction has been proposed for these[33] and related catalysts,[60] although its mechanism is not fully understood. It can be assumed that this is the mechanism involved in the cyclopropanation of *N*-Boc-indole and *N*-Boc-pyrrole (Scheme 3).

However, some of our results seem to indicate that another mechanism may be responsible, at least in part, for the insertion reaction on the heterogeneous catalyst (Scheme 3). Silica–alumina is able to stabilize Cu(I) species much better than silica,[37,38] which is in agreement with its better behaviour of $CuO_x/SiO_2–Al_2O_3$ than CuO/SiO_2 in the carbene insertion into THF,[33] a behaviour not observed in the case of the insertion into *N*-methylindane. On the other hand CuO/SiO_2 has been recently shown to be an effective Lewis acid catalyst.[61] The origin of this acidity, well evident from the IR spectra of adsorbed pyridine, traces back to the high dispersion of the copper oxide phase in this catalyst, making its particles coordinatively unsaturated.[62] Moreover, it has already been reported that the nature of the catalyst support has a marked influence on the reaction outcome of other heterogeneous Cu catalyzed C–C bond forming reactions.[63]

The lack of dimerization products (2,3-diphenylmaleate and fumarate), typical of carbene chemistry, may be due to the slow addition of diazo compound, which minimizes this side reaction. However, the addition of methyl phenyldiazoacetate in one pot leads to the same result, showing that insertion is very fast, without any induction period coming from the Cu(II) to Cu(I) reduction,[58,59] which has shown to be the rate limiting step in some heterogeneously catalyzed cyclopropanations.[64] A last piece of evidence for a Lewis acid mechanism is the different behaviour against the presence of ligands. Whereas the insertions through carbene intermediates are accelerated by bis(oxazoline) ligands,[31–33] in this case the addition of a ligand leads to the deactivation of the catalyst for indole insertion. Thus a mechanism in which Cu(II) acts as a Lewis acid and is not reduced to Cu(I) may operate in this case, with N_2 as a leaving group in an aromatic electrophilic substitution and a final migration of a proton to recover the aromaticity of indole or pyrrole (Scheme 3). In fact this mechanism would also agree with the substitution pattern observed, C3 for indole and



Scheme 3 Proposed mechanisms for insertion and cyclopropanation of indoles.

C2 for pyrrole. It is important to note that the reaction is formally and mechanistically similar to a Friedel–Crafts alkylation but with N_2 as the only concomitant byproduct and using an easily separable and reusable catalyst.

4 Conclusions

It has been shown that a particularly simple and robust copper oxide on a silica catalyst is able to promote the reaction of diazo compounds of different nature (acceptor, acceptor–acceptor, donor–acceptor) with indole and pyrrole derivatives under mild conditions. In the case of unprotected or *N*-alkyl derivatives, alkylation products are obtained, with a preference for position 3 in indoles and position 2 in pyrroles, although this preference may change depending on the substitution pattern of the heterocycle. In contrast, cyclopropanes are obtained with *N*-Boc derivatives. The catalyst has shown to be recoverable and reusable at least 5 times.

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