Homogeneous and supported copper(II) acetate as catalyst for C−O coupling reactions

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Abstract

The reactivity of copper(II) acetate as catalyst in a standard C−O coupling reaction has been systematically evaluated. Optimization of the reaction conditions resulted in a protocol involving stoichiometric amounts of reagents, a substoichiometric amount of base and 20 mol% catalyst, at 50 °C in 1,2-dichloroethane and under 1 atm O_2. Next, the reactivity of polymer-supported copper(II) acetate was evaluated. Although it is found that, in contrast to previous results obtained in related C−N coupling reactions, the polymer-supported catalyst is in this case less efficient than the corresponding homogeneous one, the catalyst turns out to be conveniently recovered from the reaction mixture by simple filtration.
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1. Introduction

Palladium-catalyzed carbon–carbon and carbon–heteroatom cross-coupling reactions have nowadays become one of the most important reaction classes in chemical synthesis [1]. Some of these reactions, most notably the Heck reaction [2], the Suzuki reaction [3] and the C−N coupling of organic halides with nitrogen-containing compounds (the so-called Buchwald–Hartwig coupling) [4] have been developed to a high degree of synthetic utility. However, since all these reactions need a palladium catalyst (albeit in extremely low amount in some cases [5]), the cost of the metal catalyst may become an issue for their technological application. Therefore, a fluorishing area of research is the quest for catalysts made out of less noble metals which exhibit comparable catalytic efficiency. Interesting results have been obtained with nickel catalysts [6], but in the last few years copper catalysts have undoubtedly taken the lead [7].

Copper is a very well-known catalyst for cross-coupling reactions, since Ullmann and Goldberg discovered at the beginning of the last century the reactions later named after them, namely the C−N coupling of aryl halides with amines or amides [8,9].

The scope of this reaction was later considerably extended to include the coupling of aryl halides and other compounds containing an N−H or O−H function [10]. However, despite extensive research in that area, the Ullmann, Goldberg and related reactions have been always plagued by the need for large amounts of copper (in the form of salts, oxides or finely divided metal) and for very harsh reaction conditions, most notably for a high reaction temperature. Therefore, as palladium catalysts much later emerged as extremely versatile catalysts also for many C−N cross-coupling reactions [4], research on copper catalysts almost subsided.

More or less at the turn of the century, however, two novel approaches have made it clear that copper-catalyzed cross-coupling reactions can be run under much milder, technologically attractive reaction conditions. First of all, it was shown that simple copper(I) complexes with diamine ligands could effect the coupling of aryl halides with nitrogen, oxygen or even carbon nucleophiles in good yields at temperatures around 100 °C [7a–c,11]. Secondly, it was demonstrated that copper(II) acetate could promote the coupling of many different organometallic compounds, most notably aryl- and vinylboronic acids, with many different compounds containing an N–H and also an O–H function, *at room temperature* [7d,12–15]; other simple copper(I) salts were later also found to be active, albeit at higher temperature [16]. In the initial reports on this reaction use of a stoichiometric amount of $Cu(OAc)_2$ was described [12], but

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more recently the C–N coupling reaction was made catalytic in copper by running it under an oxygen atmosphere [13]. We [14] and others [15] also demonstrated that polymer-supported copper(II) acetate was very effective in catalyzing this reaction and was also recyclable.

In this paper, we intend to present our results on a systematic evaluation of the catalytic potential of $Cu(OAc)_2$ in a model C–O coupling reaction, as well as on the catalytic application in this reaction of polymer-supported copper(II) acetate. Remarkably, the original reports on the application of the $Cu(OAc)_2$ system to the promotion of C–O coupling reactions between arylboronic acids and phenols [12a,b] were saluted with great interest by the scientific community, particularly in view of their application to the synthesis of diarylethers, useful intermediates or end products for which general synthetic protocols under mild conditions are highly appreciated [17]. In spite of this, copper-promoted C–O coupling reactions of this kind have remained in the following years quite underdeveloped in comparison to the corresponding C–N coupling reactions, and the possibility of using catalytic amounts of copper has to the best of our knowledge not been systematically evaluated, apart from a few scattered reports where there is brief mention that this is indeed possible [12b,13e,13f].

2. Results and discussion

We have started our investigation by evaluating the catalytic efficiency of simple copper(II) acetate in a standard C–O coupling reaction, namely the coupling of *p*-cresol with phenylboronic acid; the reaction is depicted in Scheme 1.

Copper-catalyzed C–O coupling reactions of this kind are usually run at ambient conditions, in halogenated solvents such as dichloromethane, with a stoichiometric or even over-stoichiometric quantity of $Cu(OAc)_2$, excess phenylboronic acid and excess base [12a,b]. Initially, we chose to use 10 mol% $Cu(OAc)_2$ as the catalyst, dichloromethane as the reaction medium and triethylamine as the base. The reaction time was set constant at 24 h and was not further optimized. The results are reported in Table 1.

Our first concern was to test whether a base such as triethylamine was necessary for the reaction. Indeed, we have previ-
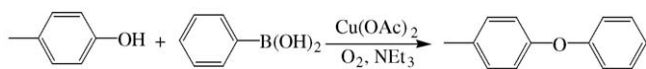
ously shown that in the C–N coupling of aromatic amines with phenylboronic acid, triethylamine acts in fact as an inhibitor of this reaction, probably because it competes for the free coordination sites at the copper centers, and that much higher conversions (albeit with lower selectivities) are obtained without the amine base [14]. However, in the case of the C–O coupling investigated in this work the presence of a base turned out to be fundamental: in fact, no conversion was observed in the absence of triethylamine (entry 1). On the other hand, a substoichiometric amount of base with respect to *p*-cresol (0.5 eq.) was found to be optimum; higher amounts decreased the yield of the reaction (compare entries 2 and 4). The effect of the dioxygen pressure was also investigated. Increasing the pressure from 1 to 5 atm caused only a marginal improvement in the reaction yield (entry 3); furthermore, the selectivity of the reaction decreased, in that formation of small amounts of a secondary product was apparent. This secondary product was identified as diphenylether, a known byproduct in this kind of reactions [18].

We then moved to analyze the effect of the reaction temperature on the catalytic efficiency of the system. Owing to the low boiling point of dichloromethane, we had however to change the reaction medium. In previous studies, *N,N*-dimethylformamide (DMF) was reported to be an alternative solvent for the reaction [13e,f]; however, the yields obtained in this solvent with our standard C–O coupling reaction under reaction conditions otherwise identical to those reported above were very low, amounting to only 15% at room temperature and 22% at 50 °C. Thus, we looked for a solvent with similar characteristics to dichloromethane but with a higher boiling point, and opted for 1,2-dichloroethane. The results obtained in this solvent are reported in Table 2.

The yield obtained at room temperature in 1,2-dichloroethane is somewhat lower than that obtained in dichloromethane (30% versus 37% yield). However, a significant increase to 40% yield is recorded upon running the reaction at 50 °C (entry 2); no

Scheme 1.

Table 1
Catalytic tests performed with $Cu(OAc)_2$ in dichloromethane

Entry	O$_2$ pressure (atm)	NEt$_3$ (mmol)	Reaction yield (%)[a]
1	1	0	0 (0)
2	1	0.5	37 (0)
3	5	0.5	42 (6)
4	1	1.0	30 (0)

Reaction conditions: 1 mmol *p*-cresol, 1 mmol phenylboronic acid, 0.1 mmol $Cu(OAc)_2$, room temperature, 24 h.

[a] The numbers in brackets indicate the diphenylether yield, see text.

Table 2
Catalytic tests performed with $Cu(OAc)_2$ in 1,2-dichloroethane

Entry	Cu(OAc)$_2$ (mol%)	T (°C)	O$_2$ pressure (atm)	Time (h)	Reaction yield (%)[a]
1	10	RT	1	24	26 (0)
2	10	50	1	24	40 (0)
3	10	83	1	24	40 (0)
4	10	50	5	24	36 (5)
5[b]	10	50	5	24	43 (4)
6[c]	10	50	1	24	38 (0)
7[d]	10	50	1	24	30 (0)
8	10	50	1	48	46 (0)
9	10	50	1	72	48 (0)
10	20	50	1	24	68 (2)
11	30	50	1	24	69 (4)
12	40	50	1	24	74 (4)

Reaction conditions: 1 mmol *p*-cresol, 1 mmol phenylboronic acid, 0.5 mmol NEt$_3$.

[a] The numbers in brackets indicate the diphenylether yield, see text.
[b] Reaction performed with 0.33 mmol triphenylboroxine and powdered 4 Å molecular sieves.
[c] Reaction performed with 0.2 mmol NEt$_3$.
[d] Reaction performed with 2 mmol phenylboronic acid.

further increase is observed by running the reaction at reflux (entry 3). An increase of the dioxygen pressure brings also in this case no substantial advantage in terms of yield and causes the formation of diphenylether as secondary product (entries 4 and 5). One of the experiments run at 5 atm was also conducted under strictly anhydrous conditions, i.e. by adding powdered 4 Å molecular sieves as well as by using triphenyl-boroxine instead of phenylboronic acid (which in solution is invariably in equilibrium with the boroxine thereupon liberating water). Use of a strictly anhydrous environment obtained upon molecular sieves addition was previously reported to be beneficial for the related C−N coupling reaction [12b]. However, only a marginal improvement in the reaction yield was observed (entry 5 versus entry 4). In this respect, it should be noted that a recent report on the coupling of arylboronic acids with benzimidazole convincingly demonstrates that this reaction is actually accelerated by an optimal amount of water [19]; thus, the role of water in these reactions could be more complex than commonly believed. A further reduction of the amount of base employed to 0.2 eq. had almost no effect on the reaction yield (entry 6), and use of excess phenylboronic acid turned out to be detrimental (entry 7). The latter observation is particularly important, since most of the previously reported protocols for this reaction as well as for the related C−N coupling reactions invariably require the utilization of excess boronic acid, which is by far the most expensive reagent. By prolonging the reaction time to 48 and 72 h it was apparent that the reaction almost stopped already after the first 24 h of reaction, the yield reaching just 48% after 72 h (entries 8 and 9). Finally, upon increasing the amount of catalyst from 10 to 20 mol% a significant improvement in yield could be achieved (entry 10). Further increases in the amount of catalyst did not lead however to comparable improvements; moreover, the formation of diphenylether as secondary product was again apparent (entries 11 and 12).

We then turned to the evaluation of our polymer-supported system. The polymer-supported catalyst was made out of a tailor-made resin based on *N,N*-dimethylacrylamide with 4 mol% methylene bis(acrylamide) as the crosslinker and 12 mol% methacrylic acid as the functional, metal binding comonomer; treatment of the resin with a solution of Cu(OAc)$_2$ in methanol resulted in a ligand exchange reaction with partial substitution of the acetates with polymer-bound carboxylate groups [14]. In our previous work on related C−N coupling reactions, we did find that this supported complex led to a superior performance in comparison to simple Cu(OAc)$_2$. In the case of the C−O coupling reaction, however, we had to realize that this was not the case, and that systematically lower yields were observed with the supported complex, both in dichloromethane and 1,2-dichloroethane and at room temperature as well as at 50 °C (Table 3, entries 1–3). We thought that this could be due to diffusional limitations to the transport of the reagents through the polymer support. However, a control test performed with a fully analogous polymer support with only 2% crosslinking and consequently with a consistently higher swelling volume yielded the same result (entry 4). Enhancing the quantity of catalyst led also in this case to a significant improvement in

Table 3
Catalytic tests performed with polymer-supported Cu(OAc)$_2$ in 1,2-dichloroethane

Entry	Solvent[a]	Cu(OAc)$_2$ (mol%)	T (°C)	Reaction yield (%)[b]
1	DCM	10	RT	14 (0)
2	DCE	10	RT	12 (0)
3	DCE	10	50	27 (0)
4[c]	DCE	10	50	29 (0)
5	DCE	20	50	44 (1)
6[d]	DCE	20	50	13 (0)
7	DCE	40	50	50 (0)
8[e]	DCE	40	50	37 (0)

Reaction conditions: 1 mmol *p*-cresol, 1 mmol phenylboronic acid, 0.5 mmol NEt$_3$, 1 atm O$_2$, 24 h.
[a] DCM = dichloromethane, DCE = 1,2-dichloroethane.
[b] The numbers in brackets indicate the diphenylether yield, see text.
[c] Reaction performed with a 2% crosslinked polymer support.
[d] Recycle of entry 5.
[e] Recycle of entry 7.

the reaction yield, which however never exceeded 50% (entries 5 and 7). Furthermore, when the recycling of the supported catalyst was attempted following separation from the reaction mixture, washing with 1,2-dichloroethane and drying in air, the productivity of the catalyst was found to decrease significantly (compare entries 5–8). A reason for the observed decrease in catalytic productivity could be the leaching of copper species from the support. However, copper analysis on the reaction mixture of the first reaction cycle after catalyst separation revealed that, although some copper was indeed released into the solution, the total amount was only 4.7% of the total copper amount in the employed catalyst charge. Thus, the explanation of the observed decrease in catalytic productivity should be that decomposition of the active catalyst takes place, presumably upon formation of inactive complex species. Experiments designed to establish the nature of such species are currently underway.

In conclusion, we have demonstrated that model C–O coupling reactions such as that between *p*-cresol and phenylboronic acid can be run with only a catalytic amount of Cu(OAc)$_2$ (20 mol% as the optimum). We have established optimized reaction conditions (1,2-dichloroethane as the solvent, 1 atm O$_2$, 50 °C, 24 h) which allow the use of stoichiometric amounts of reagents, and we have demonstrated that a substoichiometric amount of base is already sufficient to promote the reaction. In contrast to C−N coupling reactions, in which they perform better than Cu(OAc)$_2$, polymer-supported copper(II) carboxylate species are inferior catalysts for the C–O coupling reaction. The supported catalyst can be easily and almost quantitatively recovered from the reaction mixture; however, its catalytic productivity is significantly decreased upon recycling. Finally, the importance of the proper design of the polymer support for the development of such catalysts should be emphasized. In fact, a support is needed which is highly swellable in the reaction solvent and in which copper(II) acetate is molecularly dispersed as polymer-bound carboxylate. Indeed, we have also prepared a polymer-supported catalyst based on a commercial macroporous resin bearing car-

boxylate groups, namely resin Lewatit CNP 105. This catalyst turned out to be completely inactive both in C−N and C−O coupling reactions, which is probably due to the poor accessibility of the copper carboxylate species inside the polymer framework. We are currently attempting to optimize the nature of the polymer support in order to further improve both the catalytic productivity and the stability of the supported catalyst.

3. Experimental

3.1. General

All manipulations were carried out under an atmosphere of dinitrogen. The reagents were purchased from Aldrich as high-purity products and generally used as received. Solvents were dried by standard procedures and distilled under dinitrogen prior to use. GC chromatograms were taken with a Shimadzu GC-8A equipped with an OV-1701 capillary column. GC–MS was performed on a Varian Saturn 2100 T apparatus equipped with a CP-Sil 8 CB column.

3.2. Resin preparation

The synthesis of the polymer support has been reported in a previous paper [14] and it was repeated here with only slight modifications. The polymerization itself was carried out with standard protocols set up in these laboratories [20]; 8.35 g (84.4 mmol, 84 mol%) *N*,*N*-dimethylacrylamide, 1.04 g (12.1 mmol, 12 mol%) methacrylic acid and 0.62 g (4.0 mmol, 4 mol%) methylene bis(acrylamide) were mixed together and the resulting clear mixture was put in screw-cap vials and exposed to the γ-rays from a ^{60}Co source at $0.12 \, \text{Gy s}^{-1}$ at room temperature and at a distance of 22 cm for 24 h. The resulting clear transparent rod was crushed, extensively washed with methanol, vacuum dried and sieved to a particle size <180 μm. The concentration of acetic acid moieties in the resulting resin was predetermined to be 1 mmol/g.

3.3. Resin metallation

The protocol for resin metallation has been reported in a previous paper [14] and it was repeated here with only slight modifications. One gram resin was pre-swollen in 10 ml methanol for 1 day. Ten milliliters of a methanol solution of a 0.1 M Cu(OAc)$_2$ solution (1 eq. with respect to the amount of carboxylic acid groups in the tailor-made polymer) was then added. The mixture was gently shaken at room temperature for 1 day, after which time the resin was separated by filtration, washed three times with methanol and dried at 50 °C under vacuum to constant weight. The degree of Cu(OAc)$_2$ takeup by the resin was estimated to be 90% from the ICP–AAS analysis of Cu contained in the mother liquor and in the washings. The procedure was repeated with 1 g of previously dried commercial Lewatit CNP 105 resin; in this case, Cu(OAc)$_2$ takeup was found to be quantitative.

3.4. Catalytic tests

Typical procedure: 0.108 g (1.0 mmol) *p*-cresol and 0.122 g (1.0 mmol) phenylboronic acid were placed in a three-necked 100 ml round-bottomed flask equipped with a magnetic stirring bar and a septum inlet; 10 mol% copper catalyst were then added: the flask was closed, evacuated for a few minutes and then filled with dioxygen. Solvent (10 ml), 70 μl (0.5 mmol) triethylamine as well as 50 μl hexadecane as internal standard were then added and the mixture was vigorously stirred at the desired temperature for 24 h. Conversions and yields were estimated by gas chromatography.

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