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Cupreine grafted onto silica as enantioselective and recyclable catalyst for the 1,4-addition of malonate to *trans*-β-nitrostyrene†

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Preparation of silica supported cupreine (CPN) and its high catalytic performances for the asymmetric 1,4-addition of dimethyl malonate to *trans*-β-nitrotsyrene in some biomass-derived solvents (2-methyl THF, EtOAc and EtOH) are reported for the first time.

Ten years ago, the pioneer works of Deng and co-workers on *Cinchona* alkaloids bearing a 6'hydroxyquinoleine such as cupreine (CPN) or cupreidine (CPD) and their C_9-OR derivatives revealed their great efficiency for the 1,4-addition of malonate to nitroalkenes with higher enantioselectivy than their parents quinine or quinidine, respectively (figure 1).[1,2]

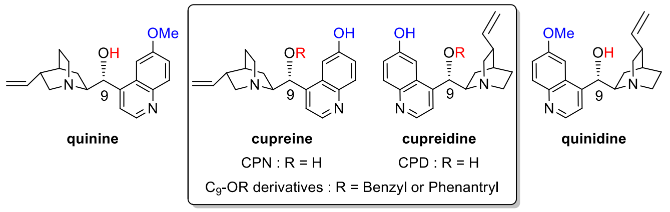


Figure 1 Structure of *Cinchona* alkaloids CPN and CPD

Afterward cupreine, cupreidine and their C_9-OR derivatives were included in the bifunctional catalyst class and proved their powerful efficiency by catalysing with high enantioselectivity and/or diastereoelectivity different conjugate additions between a large panel of partners[3] and other addition reactions (*e.g.* Friedel-Craft,[4] Henry[5] and nitroaldol reactions[6]) together with Kornblum DelaMare rearrangement.[7] Recently, Chauban and Chimni have reviewed all the asymmetric transformations catalysed by the bifunctional catalysts bearing an aromatic hydroxyl group including CPN and its C9 derivatives and proved definitively the interest given to this significant class of catalysts.[8]

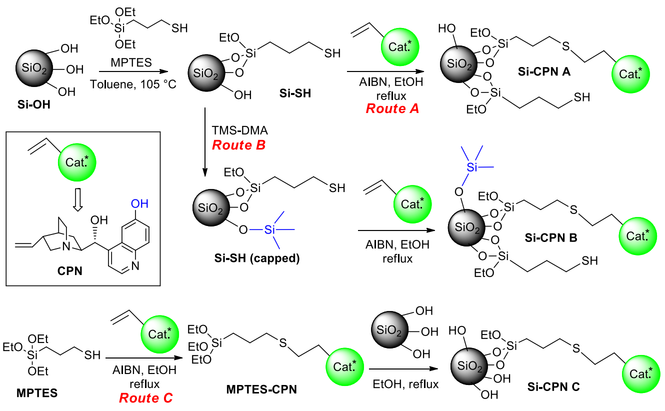
However, all the catalysts reported above have been used only under homogeneous conditions. Unfortunately, such conditions suffer from tedious work-up procedure with tricky separation of catalyst from final product leading to catalyst loss and high cost process. Organocatalyst immobilisation may overcome these limitations by allowing easier recovering of the catalyst and it's recycling. This strategy can lead to a practical and economic catalytic system since higher turnover number (TON) could be reached. Furthermore, grafted catalyst offers the opportunity to implement the catalysis under continuous flow conditions.[9]

Several *Cinchona*-based catalysts have been already grafted onto different homemade[10] or commercially available polymers.[11] Only some examples were reported concerning the grafting of *Cinchona* alkaloids as organocatalysts onto different porous inorganic supports such as silica (silica gel 60,[12] SBA-15,[13] MCM-41,[12a,13a] and Aerosil 200[14]), Fe_3O_4 magnetic nanoparticles,[15] gold nanoparticles,[16] and porous zirconium phosphonate.[17]

Depending on the *Cinchona* alkaloid catalyst and the support used, the enantioselectivity performance are mostly maintained or slightly lower compared to their homogeneous counterpart that pointed out the good behaviour of those catalysts for the immobilisation strategy. However, in general the turnover frequency (TOF) decreases for grafted catalyst due to mass transfer resistance and in addition, recycling remains often a challenge. To the best of our knowledge any *Cinchona* alkaloid bearing a 6' hydroxyquinoleine function has not been anchored onto insoluble support yet. Among all the insoluble supports already used, those based on silica have retained our attention especially for the versatility that their offer to anchor a catalyst: grafting onto preformed silica support ordered or not, as well as by using a co-condensation process. Furthermore, as residual silanol groups (Si-OH) on the silica surface could be not inert during the catalysis, a possible end-capping of those residuals Si-OH is still possible to modify the surface of this support.

Herein we report (i) the first preparation of supported CPN onto the simplest and cheapest amorphous silica support, the silica gel Si 60 Å (70 – 200 µm), (ii) the catalytic performances of the anchored CPN bifunctional catalyst for the asymmetric 1,4-addition of dimethyl malonate to the *trans*-β-nitrotsyrene especially in solvents derived from biomass as our interest is the development of new process using alternative solvents,[18] and (iii) the recycling of the supported catalysts.

CPN was readily prepared in one step from commercially available quinine[1] then grafted to the silica support through a thioether bond involving the 3-mercaptopropyl triethoxysilane (MPTES) as a linker between the catalyst and silica.[19] Based on this strategy, three alternative routes were tested to prepare different batches of Si-CPN (scheme 1); route A: the silica surface was first functionalized by mercapto groups (Si-SH), and then CPN was bound through a thiol-ene reaction performed under heterogeneous conditions using 2,2′-azobis(2-methylpropionitrile (AIBN) as radical initiator; route B involved the end-capping of the residual silanols remaining free at the surface of the silica by using *N*,*N*-dimethyl trimethylsilylamine (TMS-DMA)[20] before the immobilisation of CPN; Finally, route C: the thiol-ene reaction was first carried out under homogeneous conditions to link MPTES to CPN[21], then the adduct (MPTES-CPN) was tethered onto the silica surface after a washing step to remove unreacted MPTES.

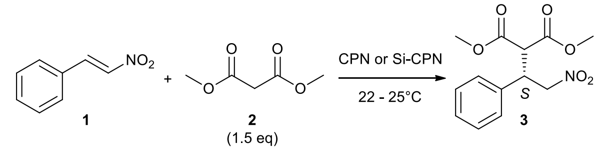


Scheme 1 Preparation of the supported Si-CPN A, B and C

All batches of Si-CPN A, B and C were characterized by classical techniques: elemental analysis (C, N and S %), thermogravimetry, BET and FT-IR analysis (See supplementary material). Elemental analysis proved a CPN loading of 0.364, 0.268 and 0.225 mmol.g^{-1} of silica for Si-CPN A, B and C, respectively. Thermogravimetric analysis performed on all Si-CPN, patently displayed two different species grafted onto silica surface: a first weight loss was observed at 300°C for the linker with SH group remaining free, while a second weight loss, consequent to the degradation of the grafted catalyst, was seen at 500°C. By comparing the N and S % from the elemental analysis, the residual SH groups remaining onto the silica surface after grafting CPN could be estimated too. The residual SH groups were most abundant for Si-CPN A (60%) and B (69%) compare to Si-CPN C (18%). Thereby, the route C offers the possibility to remove most of the residual SH groups onto the silica surface.

The asymmetric Michael addition to nitroalkene is a useful tool for the preparation of versatile optically active building blocks as intermediate in the synthesis of some biological active compounds.[1,22] The catalytic performances of supported catalysts Si-CPN A to C were thus evaluated for the asymmetric 1,4 addition of dimethyl malonate to *trans*-β-nitrostyrene as a model reaction and compared with those obtained with the homogeneous counterpart. Reactions were carried out with *trans*-β-nitrostyrene **1** (0.5 M) and dimethyl malonate **2** (1.5 eq) at room temperature in the presence of supported catalysts Si-CPN or CPN under agitation in biomass-derived solvents (Me-THF, AcOEt, EtOH) and in THF for comparison. All results are summarised in table 1.

Table 1 Catalytic performances comparison between CPN and Si-CPN A to C.



Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[a] (%) (conv[b] (%))	ee[c] (%) **3**	TOF[d]
1	CPN (10)	THF	24	88 (100)	90	0.42
2	Si-CPN A(12)	THF	62	90 (95)	87	0.13
3	Si-CPN B (27)	THF	28	97 (99)	73	0.13
4	Si-CPN C (22)	THF	72	95 (99)	80	0.06
5	CPN (10)	MeTHF	16	89 (100)	92	0.62
6	Si-CPN A(12)	MeTHF	41	89 (97)	87	0.20
7	Si-CPN B (27)	MeTHF	20	90 (94)	77	0.17
8	Si-CPN C (22)	MeTHF	20	95 (99)	88	0.22
9	CPN (10)	EtOAc	48	84 (100)	89	0.21
10	Si-CPN A(12)	EtOAc	62	90 (95)	82	0.13
11	Si-CPN B (27)	EtOAc	48	93 (97)	76	0.07
12	Si-CPN C (22)	EtOAc	72	93 (97)	83	0.06
13	CPN (10)	EtOH	24	97 (100)	57	0.42
14	Si-CPN A(12)	EtOH	30	93 (96)	60	0.26
15	Si-CPN B (27)	EtOH	21	93 (96)	42	0.17
16	Si-CPN C (22)	EtOH	48	92 (98)	54	0.09

[a] Isolated yield. [b] Conv (%) determined on crude reaction mixture by HPLC with Si-CPN or RMN-^{1}H with CPN. [c] Determined by HPLC analysis on a Kromasil 3-CelluCoat RP column. [d] Turn over frequency (mol of **3**/mol cat/h) calculated using conversion.

We were pleased to observe that the Michael addition took place with Si-CPN A (12 mol %) in THF while the reaction did not proceed during the same time in the presence of unmodified silica alone. Furthermore, the ee % of the Michael adduct **3** (*S* configured) was almost preserved (entries 1 and 2).[1] To the best of our knowledge, no conformational analysis of CPN has been investigated yet. Nevertheless, extended conformational studies of the *cinchona* alkaloids such as quinine (figure 1) have been well explored by NMR in different solvents and calculation approaches. All these analysis have proved that quinine adopts preferentially the so-called *anti*-open conformation in solution.[23] Based on the hypothesis that CPN adopts the same open conformation; three possible models for the arrangement of both reagents **1** and **2** with the catalyst CPN are shown in figure 2.

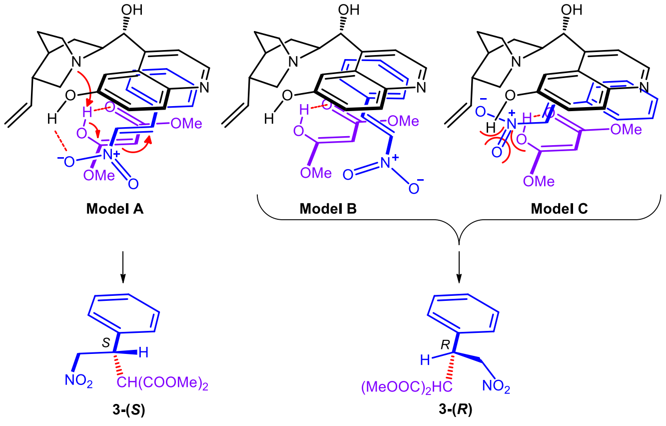


Figure 2 Postulated models for the 1,4 addition of dimethyl malonate **2** to *trans*-β-nitrostyrene **1** in the presence of CPN.

In model A we postulated that the π-stacking interaction between the π-donor quinoline ring and the π-acceptor trans-β-nitrostyrene determines the absolute configuration *S* of product **3** since only the *Si* face of the double bond of **1** remains accessible for the nucleophile attack of **2**. In contrast, both models B and C show a loss of H-bonding with loss of π-stacking interaction or a severe steric interaction, respectively.

As expected, the anchored CPN displayed same stereoselectivity and a TOF only 2.5 times lower compared to its homogeneous counterpart. As the TOF was lower with grafted catalyst Si-CPN A, the 1,4-addition using catalysts Si-CPN B and C were performed with 27 and 22 mol% catalyst, respectively. Unfortunately, with the two latter supported catalysts the ee% were slightly lower in THF, especially when the capped Si-CPN B was used (entries 3 and 4). This last observation was in accordance with results already reported for quinidine grafted onto capped Kieselgel 60.[12a,d]
Moreover, while the TOF of Si-CPN A and B were identical, that of Si-CPN C was halved. Next, we investigated the Si-CPN catalytic activity by performing the Michael addition in different biomass-derived solvents. MeTHF and AcOEt are not classically used for Michael addition however, as shown in table 1, both solvents are suitable for this reaction since 92 and 89 ee % were obtained respectively for **3** under homogeneous conditions (entries 5 and 9). Furthermore, we were delighted to observe a better TOF in MeTHF than in THF. Surprisingly the reaction was twice as long as in THF when AcOEt was used as the solvent, leading to a quite poor TOF even under homogeneous conditions (entry 9). By using Si-CPN A or C in MeTHF, the ee % were still comparable to the ones obtained with homogeneous counterpart CPN, while the ee % was always lower with the capped Si-CPN B (entries 5-8). In the presence of AcOEt, all batches of Si-CPN showed a lower catalytic efficiency compared to CPN (entries 9-12). EtOH proved to be not suitable for this reaction since the ee % of **3** decreased drastically whatever the conditions (entries 13-16). In this solvent we noticed that the Michael addition somewhat occurred at 10 % conversion without catalyst. Furthermore, we assumed that in a solvent with a strong hydrogen bond donor property such as EtOH, the arrangement between the catalyst and the reactants, based on π-stacking and hydrogen bonding,[24] is not as favoured than in an aprotic solvent giving rise to a lower enantioselectivity of the addition (figure 2). MeTHF was thus found to be the best biomass-derived solvent (ee% and TOF) giving better results than THF for the asymmetric 1,4-addition of dimethyl malonate to the *trans*-β-nitrostyrene using silica supported CPN. THF and MeTHF displayed quite similar proprieties excepting that unlike THF, MeTHF is not miscible to water,[25] a strong hydrogen bond donor solvent. Thus, MeTHF could probably not desorb the water molecules always adsorbed onto the silica surface leading to water content lower in reaction mixture. As MeTHF offered the best catalytic activities, it was selected to examine the recyclability of the supported Si-CPN (table 2). The catalysts Si-CPN were recovered by filtration after the reaction, washed then dried under vacuum before the next run.

All recovered catalysts Si-CPN A to C were able to be recycled at least three and even up to five runs without any loss of catalytic activities (Table 2). As the number of recycling could be dependent of the initial catalyst mol % engaged in the first run, the turn over number (TON) have to be considered to compare them. Thereby, thanks to recycling, all the catalysts Si-CPN nearly exhibited similar TON values around 14.

Table 2 Recycling experiments for Si-CPN A, B and C.

Entry	Run	Catalyst (mol %) Time (h)	Conv.[a] (%)	Yield[b] (%)	ee[c] (%)	TON[d]
1	1	Si-CPN A (36%)	100	95	86	2.8
2	2	16 h	99	92	86	5.6
3	3		99	96	87	8.4
4	4		99	96	84	11,2
5	5		97	94	85	**13.9**
6	6		93	90	83	16.2
7	7		65	nd	83	-
8	1	Si-CPN B (21%)	93	89	83	4.4
9	2	32 h	94	93	86	8.9
10	3		82	77	85	**12,8**
11	4		64	nd	84	-
12	1	Si-CPN C (22%)	99	95	88	4.4
13	2	20 h	97	95	87	8.7
14	3		95	91	87	**12.9**
15	4		43	nd	79	-

All reactions were carried out in same conditions than for results in table 1. [a] Conversion determined by HPLC analysis, [b] isolated yield, nd: not determined. [c] Determined by HPLC analysis on a Kromasil 3-CelluCoat RP column. [d]Turn over number (mol of **3**/mol cat) calculated using conversion.

In conclusion, we have developed a novel heterogeneous chiral catalyst by grafting CPN onto amorphous silica. Our results attested for the first time that silica is a suitable support to immobilise CPN while retaining the asymmetric catalytic performance of this bifuctionnal catalyst almost unchanged. Among all supported catalysts Si-CPN prepared, the Si-CPN A displayed the best catalytic efficiency despite the presence of residual SH groups onto the silica surface. We are now investigating the use of Si-CPN A for various applications under continuous flow conditions using a packed bed reactor.

Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental details, synthesis procedures and characterisation of Si-CPN: elemental analysis, thermogravimetry, BET and FT-IR analysis. See DOI: 10.1039/c000000x

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