Supported cobalt complex-catalysed conjugate addition of indoles, amines and thiols to α,β-unsaturated compounds†

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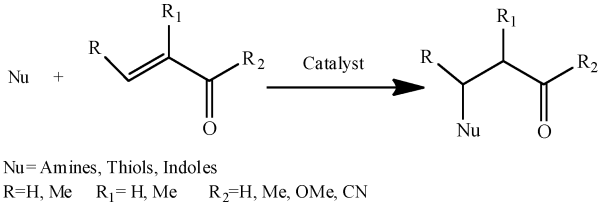
A highly active and reusable supported Co(II) complex on SBA-15 shows an excellent activity and selectivity to target products in aza- and thia-Michael conjugate additions of indoles, amines and thiols to α,β-unsaturated compounds under solventless mild reaction conditions. The Co-catalyst was also highly reusable and comparably more active than related catalysts in the reaction.

Introduction

Michael reactions of heteroatom nucleophiles to α,β-unsaturated compounds are important strategies for the formation of carbon–carbon/heteroatom bonds (Scheme 1), opening easy routes for the preparation of pivotal synthetic intermediates including bioactive compounds,[1] fine chemicals[2] and pharmaceuticals.[3]



Scheme 1 Michael addition of nucleophiles to α,β-unsaturated compounds.

Among them, aza- and thia-Michael reactions are able to provide access to a considerable range of compounds containing new C–N and C–S bonds. There are several reports of aza- and thia-Michael reactions that can be performed under mild reaction conditions (normally at room temperature for a few minutes/hours). Catalysts employed in such reactions include sulfated zirconia,[4] silica-supported Lewis acids,[5,6] polystyrene-sulfonic acid,[7] Si–Cu core–shell nanoparticles,[8] ionic liquids[9] and related acidic surfactants,[10,11] and more recently by a ferrite-anchored glutathione catalyst.[12] Uncatalysed intramolecular cyclisation of hydroxy/aminochalcones as well as aza-Michael addition have also been reported to be promoted in polyethylene glycol (PEG-400), but require relatively long times of reaction to achieve good product yields.[13] However, to the best of our knowledge, indoles remained largely unexplored as substrates in these Michael reactions due to difficulties in controlling the reaction conditions (*e.g.* acidity) to prevent side reactions including dimerisation and/or polymerization. Thus, an efficient and versatile methodology able to grant access not only to 3-substituted indoles but also to related amino- and thio-substituted compounds *via* Michael addition will be of high interest in organic synthesis.

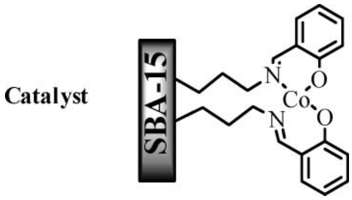
In some of our recent work, we have developed versatile Co(II) catalysts supported on mesoporous SBA-15 that exhibited remarkable activities in a wide range of processes including the chemoselective deprotection of aryl acetates,[14] the acetylation and aerobic oxidation of alcohols[15] and related oxidations of cyclohexene[16] and lignin model monomers.[17]

Following previous studies with Co(II) catalysts, we report here a highly efficient solventless Michael addition of indoles, amines and thiols to α,β-unsaturated compounds catalysed by a Co(II) complex on SBA-15 under mild reaction conditions.

Experimental

Materials: preparation and characterisation

Co(II) complex on SBA-15 material (subsequently denoted as Co/SBA-15, Scheme 2) was prepared as previously reported.[13,14] Previous studies have shown that this catalyst is highly stable under a wide range of reaction conditions, providing excellent activities in different processes.[13–16] Cobalt loading achieved for the catalyst employed in this work was found to be 0.3 mmol g^{-1}. Characterisation results of the Co/SBA-15 material have been included in the ESI.† The catalyst had a surface area of 448 m^2 g^{-1}, with a pore size of 3.6 nm and 0.77 mL g^{-1} mesoporous pore volume.



Scheme 2 Structure of the supported Co(II) complex on SBA-15.

Metal content in the materials was determined using inductively coupled plasma (ICP) in a Philips PU 70000

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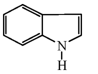
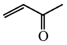
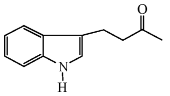
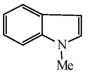
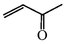
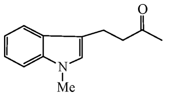
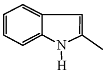
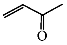
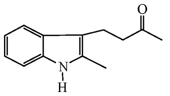
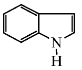
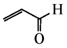
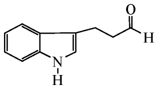
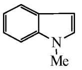
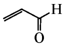
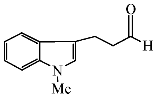
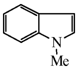
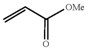
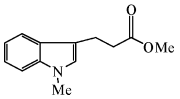
[b]Dpto. Química Orgánica, Universidad de Córdoba, Campus de Rabanales, Edif. Marie Curie, Ctra Nnal IV, Km 396, E14014, Córdoba, Spain. E-mail: q62alsor@uco.es; Fax: +34 957212066; Tel: +34 957212065

† Electronic supplementary information (ESI) available: Experimental, full characterisation of the catalyst and products. See DOI: 10.1039/b926599f

Table 1 Solventless Michael addition of indoles to α,β-unsaturated compounds catalysed by Co/SBA-15

Entry	Substrate	Enone	Product	Time/h	Yield (%)[a]
1				1.5	90
2				1.0	94
3				3.0	88
4				1	94
5				2	82
6				3	80

[a] Isolated yields.

sequential spectrometer equipped with an Echelle monochromator (0.0075 nm resolution). Samples were digested in HNO_3 and subsequently analysed by ICP.

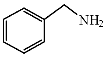
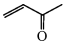
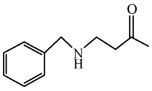
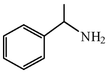
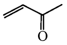
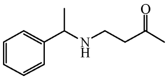
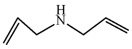
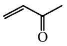
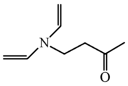
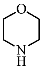
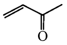
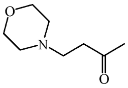
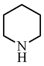
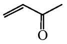
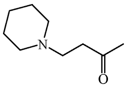
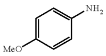
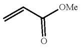
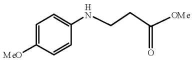
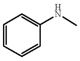
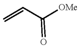
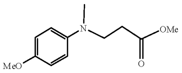
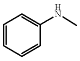
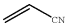
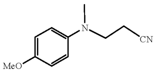
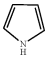
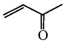
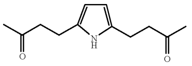
Catalytic experiments

A typical Michael reaction was performed as follows: 1 mmol indole, amine or thiol was added to a mixture of Co/SBA-15 (0.005 mmol, 0.017 g) and methyl vinyl ketone (1 mmol). The reaction mixture was then stirred at room temperature (RT) for the appropriate time. After reaction completion, CH_2Cl_2 (20 mL) was added and the cobalt catalyst was removed from the reaction mixture by filtration, rinsed twice with CH_2Cl_2 (10 mL) and reused. The filtrate was washed with water, the solvent evaporated off and the final product was isolated, in most cases in almost pure form. Further purification was carried out by column chromatography on silica gel, eluting with ethyl acetate/petroleum ether. All compounds were characterized by IR, NMR, and MS spectra (see ESI for more details†).

Results and discussion

Results of the solventless Co/SBA-15 catalysed Michael addition of indoles to α,β-unsaturated compounds are summarised in Table 1. A range of 3-substituted indoles were successfully obtained in high yields under mild reaction conditions at short times of reaction (typically 1–2 h), regardless of the substrate and the use of methyl vinyl ketone or the corresponding aldehyde or ester (Table 1).

Table 2 Solventless Michael addition of amines to α,β-unsaturated compounds catalysed by Co/SBA-15

Entry	Substrate	Enone	Product	Time/h	Yield (%)[a]
1				1.0	98
2				1.0	91
3				1.5	94
4				1.5	92
5				1.5	95
6				3	80
7				3	84
8				3	82
9				1	99

[a] Isolated yields.

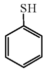
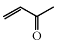
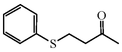
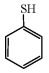
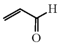
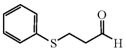
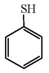
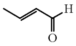
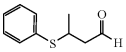
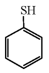
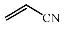
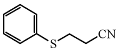
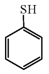
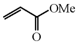
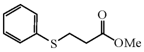
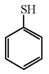
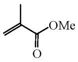
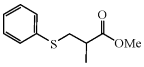
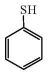
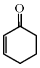
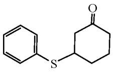
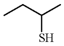
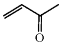
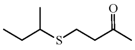
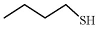
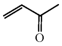
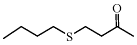
Steric effects related to the methylation in the *ortho*-position with respect to the N from the indole did not seem to be important for the Michael reaction as the corresponding product was also obtained in excellent yields at reasonable times of reaction (3 h, Table 1, entry 3).

This versatile methodology could also be extended to the use of different amines (Table 2), including secondary amines (Table 2, entries 7, 8) and pyrrole (Table 2, entry 9) acting as nucleophiles in the reaction. Excellent yields of products were obtained in all cases regardless of the nature of the amine (aliphatic or aromatic, Table 2, entries 1, 3 and 5) in 1–2 h reaction at RT. Due to the high reactivity of pyrrole, the substituted product in positions 2 and 5 was obtained as only product.

Furthermore, thiophenol as well as aliphatic mercaptans were employed as substrates to further extend the scope of the protocol to thia-Michael additions. Results included in Table 3 prove the catalyst was also highly active in the Michael addition of thiophenol/aliphatic mercaptans to methyl vinyl ketone, with quantitative yields of products typically achieved after 1 h of reaction (Table 3, entry 1).

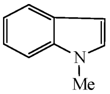
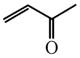
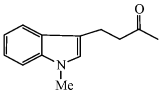
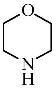
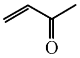
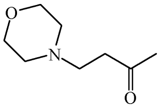
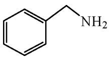
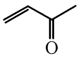
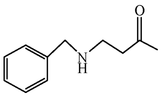
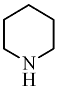
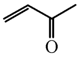
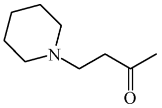
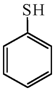
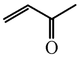
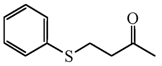
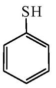
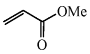
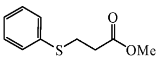
The protocol was also amenable to a range of enones, that provided moderate to very good yields of target products under

Table 3 Activity of the Co/SBA-15 material in the solventless Michael addition of thiols to a range of enones

Entry	Thiol	Enone	Product	Time/h	Yield (%)[a]
1				1	99
2				1	65
3				1.5	71
4				1	78
5				1	95
6				1.5	82
7				2	65
8				0.75	99
9				0.75	99

[a] Isolated yields.

Table 4 Activity comparison of results obtained in this work using the Co/SBA15 catalyst with related literature reports

Substrate	Enone	Product	Time/h	Yield (%)	Reference
			1.5 1.0	90[a] 93[b]	This work Ref. 11
			1.5 0.8	92[a] 90[c]	This work Ref. 4
			1.0 0.8	98[a] 90[c]	This work Ref. 4
			1.5 2.0	95[a] 78[d]	This work Ref. 6
			1.0 0.1	99 78[e]	This work Ref. 5
			1.0 0.2	95[a] 78[f]	This work Ref. 5

Reaction conditions for the different reports: [a] 0.5 mol% Co/SBA-15, RT. [b] 4 mol% SDS·HCl, RT. [c] 2 mol% SO_4^{2-}/ZrO_2, RT. [d] 10 mol% $AlCl_3/SiO_2$, 60 °C. [e] 1 mol% HBF_4/SiO_2, RT. [f] 1 mol% HBF_4/SiO_2, 0 °C.

similar reaction conditions (Table 3, entries 2 to 7). Most importantly, the Co/SBA-15 catalyst was also stable and highly reusable under the investigated reaction conditions, preserving over 90% of their initial activity after 5 reaction cycles (Fig. 1).

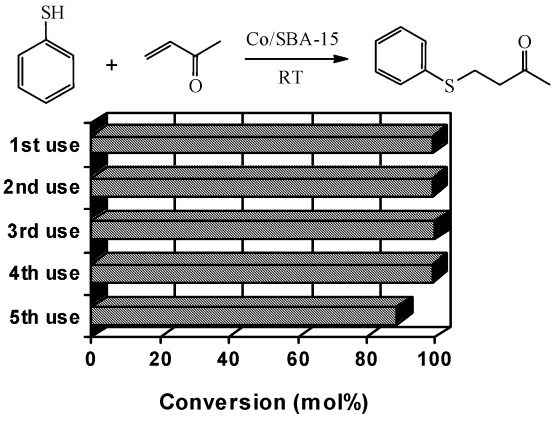


Fig. 1 Reuses of the Co/SBA-15 catalyst in the Michael addition of thiophenol to methyl vinyl ketone. Reaction conditions: 1 mmol thiophenol, 1 mmol methylvinyl ketone, 0.017 g catalyst, RT, 1 h reaction.

Further uses of the catalyst showed that, from the 6th cycle, the catalyst slightly deactivated and needed longer times of reaction (2–3 h compared to 1 h) to achieve yields of 90+%. However, no detectable metal traces in solution (<0.5 ppm) were determined by ICP of the final reaction mixture, confirming the strong coordination and stability of cobalt in the catalyst that prevented metal leaching during/after the reaction.

These results were further compared with related literature reports. Results in Table 4 show that the reported protocol, apart from being simple, versatile and environmentally sound, provides comparable and even superior yields of products in most cases under milder reaction conditions (*e.g.* less quantity of catalyst added, milder temperature of reaction, safer and more environmentally compatible catalyst, *etc.*).

This protocol is also greener compared to non-metallic methods as these normally employ significantly larger catalyst quantities and solvents,[4] high or very low temperatures (80 °C and above[7,12] or 0 °C[5]), pressures (40–180 psi[7,13]) and/or long times of reaction (>5 h) to achieve moderate yields,[13] thus offering for the first time a unique approach to the transformation of a wide range of chemically different substrates. Furthermore, the majority of such reported protocols are restricted to aza- or thia-conjugated additions with restrictions in the scope of the reaction (*e.g.* only amines, thiophenols but not linear mercaptans, *etc.*) compared to the significant range of substrates explored in this contribution.

Conclusions

We have demonstrated a Co/SBA-15 material can be a versatile and efficient catalyst for the Michael addition of a range of chemically different compounds including indoles, amines and thiols to various α,β-unsaturated compounds. This novel methodology may pave the way to the utilisation of highly active and reusable mesoporous material-supported metal complexes in multiple chemical processes.

Acknowledgements

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Notes and references

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