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9-Amino-9-deoxy-9-epi-quinine/quinidine and Acid co-Catalyst Silica-Supported for Stereoselective Batch and Flow Heterogeneous Reactions.

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9-Amino-9-deoxy-9-epi-quinine/quinidine and Acid co-Catalyst Silica-Supported for Stereoselective Batch and Flow Heterogeneous Reactions.

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Abstract

A heterogeneous, silica-based catalyst containing 9-amino-9-deoxy-epi-quinine (or quinidine) and a derivative of benzoic acid was synthesized through radical thiol-ene click reaction. The acid component allows the in-situ activation of cinchona amino group, acting as a bifunctional catalyst. The heterogenized catalysts efficiently promoted the reaction of ketones with trans-β-nitrostyrene, with diastereo- and enantioselectivity comparable to those of the homogeneous counterparts (d.r. up to 90/10 and 90% e.e.). In addition, the catalyst retained a constant activity for at least four cycles. Finally, the supported catalyst (9-amino-9-deoxy-epi-quinine/achiral acid) was employed under continuous-flow conditions. Two enantioselective Michael reactions were in sequence performed with the same homemade packed-bed reactor. The addition of cyclohexanone to trans-β-nitrostyrene provided the evaluation of optimal residence time with high level of stereoselection (2 μL/min flow rate, 83% e.e.). Furthermore, the flow reactor well performed in the preparation of warfarin (isolated yield 95%, 78% e.e. in 16 h at room temperature). The dual (chiral amine/achiral acid) solid supported system, making an even easier work-out, represents a valuable tool for green chemistry and is attractive for large scale applications.

Introduction

Solid-supported organocatalysis is one of the hot research topics in advanced organic chemistry constituting the ideal integration of a metal-free catalysis with an easy recovery and reuse of supported catalyst itself [1]. This latter aspect is particularly useful in the case of precious molecules as chiral organocatalysts that are of extreme interest in the synthesis of active pharmaceutical ingredients and chiral building blocks for fine chemistry. Usually, in the organocatalyst immobilization step, the solid support can be soluble (i.e. poly (ethylene glycol) and works in homogeneous conditions or insoluble (i.e. polystyrene or silica) producing a heterogeneous system. The second type of support offers a better

recover and recycle of catalyst (by simple filtration or centrifugation) and it is the suitable solution to transfer the catalytic system in continuous flow conditions [2]. Recently, in the field of asymmetric aminocatalysis [3], immobilization of 9-amino-9-deoxy-9-epi-cinchona derivatives (quinine as well quinidine) has received great attention due to their great versatility and high levels of enantiodiscrimination shown in different enamine or iminium ion [4] organocatalyzed reactions. In 2012, cinchona-based primary amines have been supported on polyacrylonitrile [5] and on zirconium phosphonate [6] and employed in aldol reactions. In 2015, two papers reported the potential of supported 9-amino-9-deoxy-9-epi-quinine on different matrices as recyclable catalysts in batch conditions [7, 8]. The authors investigated the Michael addition of aldehydes or ketones to trans-β-nitrostyrene and the dienamine activation of α,β-unsatured carbonyl compounds [7]. The same year, two papers reported the development of a packed-bed reactor containing supported amino-quinine catalyst suitable for continuous flow applications [8, 9]. In one case, the flow reactor operated for almost 200 h producing 1 g of product with constant stereoselectivity (e.e. higher than 90%) [8]. In the second application, a small library of enantioenriched Michael adducts was sequentially prepared in flow mode [9]. Regardless of the way in which these catalysts are used (in homogeneous or heterogeneous phase), the cinchona-based primary amines require the presence of a Brønsted acid co-catalyst, which activates the catalytic machine. Several acids differing in structure and strength have been used like acetic acid, trifluoroacetic acid, benzoic acid and its derivatives, organophosphoric acid just to list a few reported in the herein cited references. Remarkable to note, if the presence of any acid enhances the activity of the catalytic system, the use of a specific chiral acid can contribute, in a synergic way, to the stereocontrol of reaction products [10]. Here we report the synthesis of supported catalysts featuring both chiral primary amine cinchona alkaloids and achiral Brønsted acid covalently bonded to mercaptopropyl silica. The idea of presented work moved from the interest in the production of tools enabling synthesis and purification steps of chiral target compounds specifically related to asymmetric amino-catalytic systems. As reported in **scheme 1**,

currently only the catalyst can be removed by filtration from the crude of reaction. Here, we would demonstrate that the heterogeneous system can be implemented by anchoring on the same solid support also the acid co-catalyst. In this way, two components by filtration are eliminated during work-up of heterogeneous batch reaction. In addition, the potential use of the new solid support in flow mode is greatly simplified.

Scheme 1.

The supported catalysts were fully characterized by elemental analysis, FT-IR and solid-state NMR experiments in order to define the coverage and structural proximity of each component. The catalytic activity, catalyst recovery and its recycle were evaluated in the Michael addition of cyclic ketones to trans-β-nitrostyrene. Finally, the supported 9-amino-9-deoxy-9-epi-quinine/benzoic acid catalyst was employed under continuous-flow conditions.

Results and discussion

As proof of concept, a catalytic system consisting of 9-amino-9-deoxy-9-epimers of cinchona alkaloids (**1** or **2**) and a derivative of benzoic acid **3** was chosen as starting platform. Mesoporous spherical silica was employed as solid support to incorporate the different grafted functions. Many works reported on the use of silica as support to covalent bond the catalysts and cooperative catalysts [12]. In fact, mesoporous and nanoporous silica offer high surface area, mechanical stability, robustness and an easy surface multi-steps modification of silanols with organosilanes. Even a control of surface modification results facilitated with solid-state ^{13}C and ^{29}Si NMR experiments [13].

Preparation and characterization of supported catalysts.

In this study, the catalyst has been obtained by two-step radical thiol-ene click reaction between the double bond of each catalytic component and mercapto activated silica (**scheme 2**). 9-Amino-9-deoxy-

9-epiquinine **1** and 9-amino-9-deoxy-9-epiquinidine **2** were obtained as described in [14]. Mercaptopropyl silica gel MPSG was obtained by reacting (3-mercaptopropyl)trimethoxysilane with silica particles in dry toluene for 20 h at 60 °C [15]. The commercially available 4-(but-3-enyloxy)benzoic acid **3** was anchored to silica bound thiol groups in the presence of AIBN as radical initiator (**scheme 2**, **a**), and the unreacted thiol groups of Co-Cat have been eventually derivatized with the proper chiral amine catalyst (Cat) under the same conditions giving **Cat-Co-Cat-QN 4** and **Cat-Co-Cat-QD 5**, respectively (**scheme 2**, **b**). As additional step, only for catalyst **4**, a quenching procedure to inactivate the residual thiol groups was performed by using 1-hexene (catalyst **6**).

Scheme 2

FT-IR spectroscopy has been used to quickly monitor the outcome of each reaction step (Supplementary material). As reported in **figure S1**, FT-IR spectra of intermediate Co-Cat and final Cat-Co-Cat show bands at 1693 (COOH), 1609 and 1512 cm^{-1}(aromatic rings) confirming the presence of surface bound **1**-**3** fragments. A more detailed characterization of supported mixed catalysts was obtained by elemental analysis (**table 1**). The density of organic fragments was calculated from % S, %C and %N for MPSG, Co-Cat and Cat-co-Cat respectively (**table 1**). Inspection of coverage values shows that i) chiral amine/acid co-catalyst molar ratio is 1 to 3 (i.e. 160 vs 464 μmoles/g matrix) and ii) up to 90% of the thiol groups (2.56 of 2.68 μmoles/m^2) have been derivatized during steps a) and b) (**scheme 2**). In addition, coverage values of MPSG calculated from either carbon or sulfur loading (955 and 727 μmoles/g of silica respectively), indicates the presence of residual unhydrolyzed methoxysilane fragments, in agreement with ^{13}C CPMAS NMR findings (see later).

Table 1

Figure 1

According to elemental analysis results for Co-Cat and Cat-Co-Cat, the average distance between anchoring sites of the acidic fragments in Co-Cat is approximately 9 Å. On the other hand, the distance between the anchoring sites of quinine or quinidine fragments in Cat-Co-Cat is around 16 Å. These average values were calculated from the starting surface area of the silica matrix (300 m^2/g) and the amount of acid (1.88 μmole/m^2) and quinine or quinidine (0.68 and 0.63 μmole/m^2). Considering the length and flexibility of the thioalkyl spacers, the distances are reasonable for productive interaction. The structural characterization of supported catalysts was completed by using solid-state NMR techniques: magic angle spinning (^{29}Si MAS-NMR) and cross-polarization (^{29}Si and ^{13}C CPMAS NMR) experiments. ^{13}C CPMAS NMR spectra of modified silica after each reaction step of catalyst **4** were acquired and reported in **figure 1**. Mercaptopropyl silica MPSG gave two characteristic signals at 10.5 ppm and 27.3 ppm (see **figure 1**, spectrum a) and related assignments in schematic structure) corresponding to the methylene units of the propyl chain. As predicted by elemental analysis, the signal at 50.5 ppm indicates the presence of methoxy groups due to unhydrolyzed methoxysilane bonds or in addition to residual adsorbed methanol employed as washing solvent. In fact, the amount of absorbed methanol is also dependent on free unreacted silanols [16, 17]. The presence of acid co-catalyst in the derivatized silica obtained in step a) was confirmed by new signals recorded on ^{13}C CP-MAS NMR spectrum (**figure 1**, spectrum b): 68.1 ppm (-CH2-O-Ar, C 7 in the assigned structure), 114, 122, 132.8, 164.3 ppm (aromatic ring carbons, C8-13) and 173.5 ppm (carboxylic acid, C14). The spectrum of Cat-co-Cat-QN (**figure 1**, spectrum c) shows, in the aromatic region, signals due to the quinoline portion of amino-quinine while the signals of quinuclidinic moiety span between 20 and 70 ppm. Specifically, signals at 40.7, 101 and 159 ppm ascribed to C20, C33 and C34 respectively, promptly characterize Cat-co-Cat with respect co-Cat sample. Detailed assignment of all spectra is reported in **table S1** [18]. **Figure 2** shows ^{29}Si CPMAS NMR spectra of bare silica (a), MPSG (b), Co-Cat (c), and Cat-Co-Cat-QN (d). The spectrum of bare silica shows the signals of Q^2 units due to geminal silanol groups at -91 ppm, Q^3

units due to isolated silanol groups at -101 ppm, and bulk siloxane Q^4 units observed at -110 ppm (the superscripts indicate the number of Si-O-Si bonds). The spectra of MPSG, Co-CAT, and Cat-co-Cat show the typical profile of surface derivatization with organic fragments. Compared to the starting silica where only Q^n signals are present, the main difference is the appearance of T^n signals (T^1, T^2 and T^3) indicating the presence of silicon atoms directly bound to carbon atoms.

Figure 2

Figure 3

Because in CPMAS spectra the peaks intensity is modulated by transferring the magnetization from hydrogen atoms to silicon atoms, ^{29}Si CPMAS spectra recorded at a given contact time cannot be used for signal quantification. However, ^{29}Si MAS spectra collected with a suitable long recycle delay can be used for quantitative analysis of surface grafting. **Figure 3** shows ^{29}Si MAS spectra of bare silica (a), MPSG (b), Co-Cat (c), and **Cat-co-Cat-QN 4** (d), where deconvoluted spectra are superimposed to experimental ones. The spectral deconvolution gave integrals Ii for quantitative analysis, which are reported in **table S2**. Beside resonances due to Q^4 and Q^3 units, samples MPSG, Co-Cat, and Cat-Co-Cat show also resonances of trifunctional silanes: reagent geminal silanol groups (T^1 units), reagent isolated silanol groups (T^2 units), and reagent siloxane moieties (T^3 units). Specifically, sample MPSG exhibits T^3, T^2, and T^1 signals at -65.6, -56.9, and -49.0 ppm. Sample Co-Cat shows T^3, T^2, and T^1 signals at -64.5, -56.1, and -48.4 ppm. Eventually sample **Cat-Co-Cat-QN 4** shows resonances T^3 at -66.6, T^2 at -58.1, and T^1 at -48.4 ppm. Integrals obtained by spectral deconvolution (see **table S2**) show that silanol groups Q^2 and Q^3 decreased upon derivatization, in fact the ratio $[I(Q^2) + I(Q^3)]/I(Q^4)$ was 0.35 in bare silica whereas it decreased down to 0.21 in MPSG, 0.22 in Co-Cat, and 0.23 in Cat-co-Cat. Focusing on derivatized silanols of MPSG, the total surface coverage was estimated to be 6.2% of bare silica corresponding to 25% of all suitable silanols (Q^2 + Q^3). The coverage does not change after the

subsequent reaction steps (7.0% in sample co-Cat, and 6.9% in sample Cat-co-Cat) proving no collateral reaction sites are present. In addition, a slight change of the intensity of T^n silicon signals during the derivatization steps was recorded. In particular, the increase in $\%T^3$ and the concomitant decrease in $\%T^2$ (**table S3**) are consistent with the increased step-by-step cross-linking between silica and unreacted methoxysilane providing a more stable matrix.

Catalytic activity.

Catalyst **4** was tested in the Michael addition of ketones to trans-β-nitrostyrene. This reaction, has been originally reported by Connon and McCooney in 2007 [4f] and then in 2015 transferred on heterogeneous phase employing the solid supported amine chincona catalyst and maintaining the acid co-catalyst in solution [7, 8]. At the beginning, cyclohexanone was chosen to evaluate the activity of **Cat-Co-Cat-QN 4** in different working conditions (**scheme 3** and **table 2**).

Scheme 3

Before the evaluation of catalytic activity, we developed an analytical HPLC method to monitor reaction progress and quantify both yield and diastereomeric ratio (d.r.) of products in a single run. The area ratio of diastereoisomeric pair was comparable with the ratio of corresponding ^{1}H-NMR signals indicating identical UV molar extinction coefficients of the diastereoisomers (see entries with double note c) and d) in **table 2** and corresponding ^{1}H-NMR and HPLC data in Supplementary material). Thus, it was possible to determine the yield of reaction as sum of two areas. The equation $y= 3*10^6x$ ($R^2 = 0.995$) has been extrapolated from the corresponding concentration/area plot of standard solutions and the reaction yields found for each experimental condition were reported in **table 2**.

Table 2

In addition, for entries 1-4 and 7, the products were isolated by semi-preparative HPLC giving isolated yield values slightly lower than calculated ones (**table 2**). In all reactions, 30% of catalyst loading and cyclohexanone/nitrostyrene molar ratio 5/1 have been maintained. The only exception, entry 7, required a 6-fold amount of ketone to efficiently disperse the solid catalyst (molar ratio 30/1). Inspection of entry 1 in **table 2** shows that results are comparable to those obtained by using the solid-supported amino-quinine and the acid co-catalyst in solution [7, 19]. In fact, in the same working conditions excepting the non-supported benzoic acid, the reaction provided the desired product with 83% e.e., 87/13 d.r. and 65% of yield. Water inhibits the reaction (entry 6), while dichloromethane gives the highest values of % e.e. and d.r. at the expense of a lower yield (37%, entry 4). A good yield (70%, entry 7) is obtained in the absence of solvent with acceptable enantiomeric excess. Increasing temperature and reducing reaction time (40°C and 24 h) has little effects on the reaction outcome. Reactions 4 and 7 were replicated (4-Q and 7-Q) by using the end-capped catalyst 6. The results show similar yields (37% and 65% for 4-Q and 7-Q, respectively) and slightly lower performances in terms of diasteromeric ratio and %e.e. (87/13, 82% for 4-Q and 91/9, 80% for 7-Q). These data indicate a negligible interference of the small fraction of residual thiol groups (10% based on elemental analysis) on reaction progress. In order to further explore the scope of this catalytic machine, two additional ketones were included in the screening: cyclopentanone and tetrahydropyranone (entries 11 and 12). In both cases, HPLC analysis helped us in the evaluation of catalytic activity (see Supplementary material). Results are collected in **table 3**. Tetrahydropyranone furnished the product in high %e.e. and diastereoisomeric ratio after 5 days with modest yield (in ref. 4f the same substrates in homogeneous reaction produced 90% of yield after 10 days), while cyclopentanone reacted with lower stereoselectivity. As final point in the addition of ketones, the effect of catalyst loading was checked comparing the results of reactions 7 and 11 with those obtained by using 15 mol % of same catalyst. Stereochemical preferences were confirmed but a decrease

in yield was recorded (see **table S3**), so the initial content of catalyst was maintained in the following evaluations.

Table 3

Finally, the evaluation of catalytic performance was also extended to the addition of a α–substituted aldehyde, namely cyclohexanecarboxaldehyde, to trans-β-nitrostyrene. Unfortunately, all working conditions afforded too low yields (10-30%). However, remarkable results on reaction stereocontrol were obtained providing high enantiomeric excesses (79% - 85%). Details of experiments are reported in **table S4** of Supplementary material. Despite the single aldehyde checked, we gratifyingly demonstrated the potential of this new catalytic system with the second important source of carbonyl compounds as substrates typically involved in the Michael additions via enamine activation.

Quinine vs Quinidine.

In line with the **Cat-Co-Cat 4**, we evaluated the solid supported catalyst based on the 9-amino-9-desoxy-9-epi-quinidine, **Cat-Co-Cat 5**. Our synthetic procedure ensures reproducible media in terms of loading of organic fragments. In fact, coverage values in **table 1** highlights that **4** and **5** have the same acid/amine ratio allowing a correct comparison of the two catalytic materials. In details, cyclopentanone and cyclohexanone were employed in the same conditions as reported in **table 2**. Compared to catalyst **4**, the quinidine-based support **5** showed lower yield, similar diasteromeric ratio and lower e.e. in both cases (**table 4**). In addition, as expected for a pair of pseudo-enantiomeric compounds, the two catalysts showed an inverted stereochemical outcome (**figure S2**).

Table 4

Catalytic recycling.

One of the major goals of supported catalysts is their easy recovery and active recycle. In this study, supported catalyst **4** was isolated by centrifugation and recovered after drying under vacuum for 1h at 50°C before reuse. Recovery was almost quantitative after each recycle as reported in **table 5**. Unfortunately, a loss in productivity was progressively observed already at the first recycle (Batch A). The decrease in yield during recycle steps is already reported in literature [7, 20], but a reactivation of the catalysts was obtained after washing whit an acidic solution. In this case, the additional washing with benzoic acid in methanol (5% w/v) before the wash with dichloromethane, as tentative to reactivate the catalyst doesn't offer remarkable results (Batch B). While further investigations are required to elucidate the inactivation of supported acid-assisted catalyst [21], we note that residual activity persists until the 4th reuse. On the other hand, after three consecutive cycles performed at constant reaction time, no decrease in product stereochemical purity (%e.e. and d.r.) was observed attesting a good robustness.

Table 5

Reactions under flow conditions.

Better results were obtained moving from batch to flow conditions. In detail, the "in flow" ability was explored with two different substrates: a cyclic ketone and an α,β unsaturated ketone. A packed-bed flow reactor (**FR**) was prepared using a 100 x 4.6 mm L x i.d. stainless steel HPLC column containing 900 mg of catalyst **4** (0.144 mmol) and having a void volume V_0 = 1.18 mL. Reaction in **scheme 2** was performed at two different flow rates of 5 and 2 µL/min, corresponding to residence times of 236 and 590 min, respectively. After 19 h, a 4.4-fold **FR** productivity increase was observed moving from 5 to 2 µL/min (**figure 4-A**). Then, the synthesis of the chiral anticoagulant drug warfarin was realized in continuous starting from 4-hydroxycoumarin and 4-phenyl-3-buten-2-one [22]. This reaction proceeds via iminium ion and it is favoured by an excess of acid co-catalyst. The **FR** afforded warfarin (product 10 in **figure 4-B**) in 16 h with total conversion of 4-hydroxycoumarin (isolated yield 97%) and 78% of

enantiomeric excess. The two reactions were easily conducted in a sequential manner simply washing the reactor before the change of feed of different reagents.

Figure 4

Conclusions

In summary, we have developed a catalyst containing both chiral primary amine cinchona alkaloid and its achiral acid co-catalyst covalently bonded to the same activated silica support. We demonstrated the potential of in-situ activated acid/basic catalyst in the addition of cyclic ketones to trans-β-nitro-styrene. The catalytic machine promoted good yields and high stereocontrol affording final products with enantiomeric excesses up to 85%. Moreover, supported catalyst has been reused four cycles with constant and high stereoselectivity providing an easy work-up and lower environmental impact when used without solvent. Finally, the versatility of our novel catalytic system was attested in continuous-flow conditions. Enantioselective Michael addition of 4-hydroycoumarin to 4-phenyl-3-buten-2-one was performed producing the chiral drug warfarin with 78% e.e. and total conversion of its 4-hydroycoumarin precursor. These preliminary results open interesting possibilities for the heterogeneous asymmetric aminocatalysis in large-scale applications as well in flow reactions.

Experimental Section

Materials

9-Amino-9-deoxy-9-epiquinine (**1**) and 9-amino-9-deoxy-9-epiquinidine (**2**) were obtained, as described in [14]; Lichroprep silica (pore size 100 Å, particle size 25-40 μm, and specific surface area 300 $m^2 g^{-1}$) was purchased from Merck (Darmstadt, Germany). All reagents and solvents, HPLC and ACS grade, were purchased from Sigma Aldrich (Milano, Italy). HPLC gradient grade solvents were filtered on 0.45

μm Omnipore filters (Merck Millipore, Darmstadt, Germany), prior to use. All reagents were used without further purifications.

General methods

The derivatization of silica was carried out in a laboratory modified rotavapor, with the reaction flask connected to a solvent condenser, a solvent collector, and an argon inlet. Mixing was obtained by spinning the flask around its axis, providing a homogeneous dispersion and limiting particle breaking.

Synthesis of supported catalysts **4-6**

1-Preparation of mercaptopropyl‑Silica Gel: 14.5 g of silica, previously dried at reduced pressure (0.1 mmHg at 120 °C for 2 h), was dispersed in 130 mL of dry toluene at 60 °C. A solution of (3-mercaptopropyl)trimethoxysilane (39.7 mmol, 7.5 ml, $C_6H_{16}O_3SSi$; Mw: 196.34; d:1.039 g/ml) in 25 mL of dry toluene was added dropwise over 20 min. The reaction was stirred for 20 h at 60 °C under argon atmosphere. The modified silica, MPSG, was isolated by filtration, washed with toluene, methanol, and dichloromethane (250 mL each), and then dried at reduced pressure (0.1 mmHg; T: 60 °C), until the weight was constant (16.06 g). FT-IR (KBr) 3448, 2947; 2853; 1105; 804 cm^{-1}. Elemental analysis: 4.59 % C; 1.11 % H; 2.33 % S, corresponding to 727 μmoles of substrate per gram of modified silica or 2.68 μmol/m^2 (based on S).

2-Anchoring of the co-catalyst on MPSG: 4-(3-butenyloxy)-benzoic acid (**3**, $C_{11}H_{12}O_3$; Mw: 192.21; 1.10 g; 5.72 mmol) was dissolved in 8 mL of methanol (previously degassed with helium) under nitrogen atmosphere. Then 11.1 g of MPSG-silica was dispersed in the solution and AIBN ($C_8H_{12}N_4$, Mw: 164.21, 20 mg) was added to the reaction flask for three times (at the beginning, after 2 h and 4 h). The reaction was heated to refluxed and stirred for 6h. Co-Cat was filtered, washed with dichloromethane and methanol, then dried up to constant weight (11.89 g). FT-IR (KBr) 3450, 2950, 1693; 1609; 1512; 1100, 806 cm^{-1}. Elemental analysis: 9.31 % C; 1.56 % H; 2.37 % S, corresponding to 464 μmoles of substrate

per gram of modified silica or 1.88 μmol/m^2 (based on C). Unreacted acid **3** was recovered (confirmed by MS-ESI, $[M - H]^-$ = 191.21 and ^{1}H-NMR).

3-Preparation of Cat-co-Cat: Cinchona alkaloid derivative, **1** or **2** ($C_{20}H_{25}N_3O$; Mw: 323.24; 2.50 g; 7.73 mmol), was dissolved in 8 mL of methanol (previously degassed by helium sparging) under nitrogen atmosphere. Then 8.34 g of Co-Cat was dispersed in the solution and AIBN (15 mg) was added to the reaction flask for three times (at the beginning, after 2 h and 4 h). The reaction was heated to refluxed and stirred for 6h. Silica Cat-Co-Cat was filtered, washed with dichloromethane and methanol, then dried up to constant weight. Unreacted amine was recovered (confirmed by ^{1}H NMR). **Cat-co-Cat-QN 4** from 9-Amino-9-deoxy-9-epiquinine. FT-IR (KBr) 3451, 2948, 2856, 1692; 1608; 1100, 805 cm^{-1}. Elemental analysis: 12.66 % C; 1.80 % H; 0.68 % N; 2.52 % S, corresponding to 160 μmoles of substrate per gram of modified silica or 0.68 μmol/m^2 (based on N). **Cat-co-Cat-QD 5** from 9-Amino-9-deoxy-9-epiquinidine. FT-IR (KBr) as for **4**. Elemental analysis: 12.47 % C; 1.78 % H; 0.64 % N; 2.50 % S, corresponding to 153 μmoles of substrate per gram of modified silica or 0.65 μmol/m^2 (based on N).

4-Quenching of residual mercapto-groups: 5.83 g of **Cat-Co-Cat 4** was added to a solution of 1-hexene (90 μl, C_6H_{12}, Mw: 84.16; 0.76 mmol; d: 0.673 g/ml) in methanol (30 ml). AIBN was added twice at the begging and after two h (5 mg). Overall, the mixture was mechanically stirred and heated to reflux for 3 h. The **Cat-Co-Cat 6** was isolated by filtration, washed with dichloromethane and methanol, and then dried up to constant weight. Elemental analysis: 12.33 % C; 1.82 % H; 0.62 % N; 2.26 % S.

Flow reactor specifications

FR was prepared by filling a stainless steel HPLC column (i.d. 4.6 mm, L 100 mm, V 0.75 mL) with supported cooperative catalyst (900 mg, 0.144 mmol, 0.12 M). Then it was wetted through a syringe pump with 2 mL of toluene at a flow rate of 2 μl/min. Void volume V_0 of **FR** was measured experimentally by picnometry (THF and $CHCl_3$ were employed) to be V_0 = 1.18 mL. *Reaction via*

enamine in flow: A syringe pump was charged with 3 mL of a toluene solution of reagents (0.14 M trans-β-nitrostyrene, 0.68 M cyclohexanone) was fed to the reactor at room temperature. Two different flow rates were evaluated (5 µl/min and 2 µl/min). The **FR** worked globally 50 h. Only a single wash with toluene (1.5 mL) was used between the two reactions at different flow. The product at the way-out of the reactor was collected at room temperature. The conversion into the desired product was determined by HPLC of the crude mixture. The enantiomeric excess of the final product was determined by HPLC on chiral stationary phase. *Reaction via iminium ion in flow*: A syringe pump was charged with 2 mL of a THF solution of reagents (0.12 M 4-hydroxycumarin, 0.60 M benzylideneacetone), and was fed to the reactor at the indicated flow rate (2 µl/min) at room temperature. The **FR** worked for 16 h. Subsequently the flow reactor was washed with 1 mL of THF at the same flow rate. The product at the way-out of the reactor was collected at room temperature. The conversion of 4-hydroxycumanrin into the desired (-/+)-warfarin was determined by ^{1}H NMR of the crude mixture. The enantiomeric excess of the final product was determined by HPLC on chiral stationary phase.

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Keywords: Aminocatalysis; supported catalyst; asymmetric catalysis; flow reaction.

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[18] The assignments were also confirmed by in solution ^{13}C-NMR of precursor (**3**) and the 9-amino-9-deoxy-9-epi-quinine (**2**). ^{13}C-NMR ($CDCl_3$, 75 MHz) of (**3**): 33, 68, 113, 117, 132, 133, 166, 172 ppm. ^{13}C-NMR ($CDCl_3$, 75 MHz) of (**2**) in references [14, 8].

[19] Cat-Co-Cat catalyst **4** has been compared with 9-amino-9-deoxy-epi-quinine bonded on the same silica without the acidic component (catalyst loading: 392 μmoles/g matrix). The reaction in scheme 2 was performed with benzoic acid in toluene solution (acid/amine 1.2/1 molar ratio). The product was

obtained with diastereomeric ratio of 89/11, enantiomeric excess 85% and yield of 45-55%. All data were acquired from HPLC analysis.

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[21] Elemental analysis done on catalyst **4** after two reuses provided content of nitrogen and sulfur similar to the previous ones (error +0.22% and +0.10% respectively). The carbon content was increased of 1.1%.

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Figure/scheme captions.

Scheme 1. Aim of our work in a graph.

Scheme 2. Synthesis of supported catalyst. a) **3**, AIBN, methanol, 60°C, 8h; b) 1 or 2, AIBN, methanol, 60°C, 8h.

Figure 1. ^{13}C CPMAS NMR spectra of MPSG (a), Co-Cat (b), and **Cat-Co-Cat-QN** (c). Additional schematic structure and assignments were included.

Figure 2. ^{29}Si CPMAS NMR spectra of bare silica (a), MPSG (b), Co-Cat (b), and Cat-Co-Cat-QN (d). Schematic structures of silicon network are reported.

Figure 3. ^{29}Si MAS NMR spectra of bare silica (a), MPSG (b), Co-Cat (c), and Cat-Co-Cat (d). Deconvoluted spectra are superimposed to experimental ones.

Scheme 3. Reaction model.

Figure 4. Catalytic activity under flow conditions. A) Evaluation of two residence times. B) Synthesis of warfarin.

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Table 1. Elemental analysis and coverage values (surface area of starting silica: 300 m^2/g). Note a = n. groups/nm^2

Material	%C	%N	%S	µmoles/g matrix	µmoles/m^2
MPSG	4,59	-	2,33	727 (S)	2,68(1,61)[a]
Co-Cat	9,31	-	2,37	464 (C)	1,88 (1,13)
Cat-Co-Cat-QN (**4**)	12,66	0,68	2,52	160 (N)	0,68 (0,41)
Cat-Co-Cat-QD (**5**)	12,47	0,64	2,50	153 (N)	0,65 (0,39)

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Table 2: Screening of working conditions for reaction of **scheme 2** by using **Cat-Co-Cat-QN 4**. Notes:

a) Isolated yield; b) Calculated yield; c) Determined by ^{1}H NMR; d) by RP-HPLC.

Entry	**%Yield**	**Solvent**	**Time/ Temp.**	**d.r.**	**%e.e**
Ref. 7	65[a)]	toluene	48 h/r.t.	87/13	83
1	42[a)]; 48[b)]	toluene	48 h/r.t.	87/13[c)] 88/12[d)]	85
2	42[a)]; 45[b)]	toluene/MeOH 95/5, v/v	48 h/r.t.	78/22[c)] 80/20[d)]	75
3	50[a)]; 56[b)]	toluene/MeOH 98/2, v/v	48 h/r.t.	90/10[c)]	85
4	32 [a)]; 37[b)]	DCM	48 h/r.t.	92/8 [c);d)]	91
5	10[b)]	THF	48 h/r.t.	90/10[c)]	83
6	no reaction	H_2O/MeOH 90/10, v/v	48 h/r.t.	-	-
7	66[a)]; 70[b)]	NEAT	48 h/r.t.	87/13[c);d)]	83
8	66 [b)]	toluene/MeOH 98/2, v/v	24h/40°C	84/16[c)]	79
9	32 [b)]	MTBE	24h/40°C	82/18[c)]	78
10	24 [b)]	$CHCl_3$	24h/40°C	88/12[c)]	87

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Table 3: Cyclic ketones added to β-nitrostyrene. Solvent toluene/methanol 98/2 v/v, T room, 48h (5 days for **12**, see text).

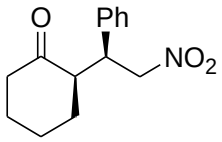
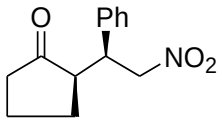
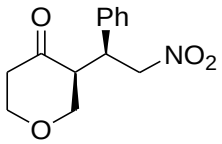
Code	Product	Yield %	d.r.	% e.e.
3	 (**7**)	56	90/10	85
11	 (**8**)	70	67/33	10
12	 (**9**)	30	84/16	91

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Table 4: Catalyst **5** vs catalyst **4** performances. Neat, T room, 48h.

ketone	catalyst	yield %	d.r.	%e.e.
	**4**/QN	66	86/14	83
	5/QD	39	77/23	70
	**4**/QN	40	76/24	21
	5/QD	25	75/25	2

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Table 5: Recycling catalyst. The % e.e. after 3rd cycle was not determined due to the low activity.

Recycle	% yield	d.r.	% e.e.	Recovery
Batch A	66	86/14	83	97%
1° recycle	39	85/15	74	98%
2° recycle	15	86/14	82	97%
3° recycle	8	89/11	n.d.	96%
Batch B	56	90/10	85	98%
1° recycle	32	87/13	81	96%
2° recycle	10	88/12	79	97%
3° recycle	2	89/11	n.d.	89%

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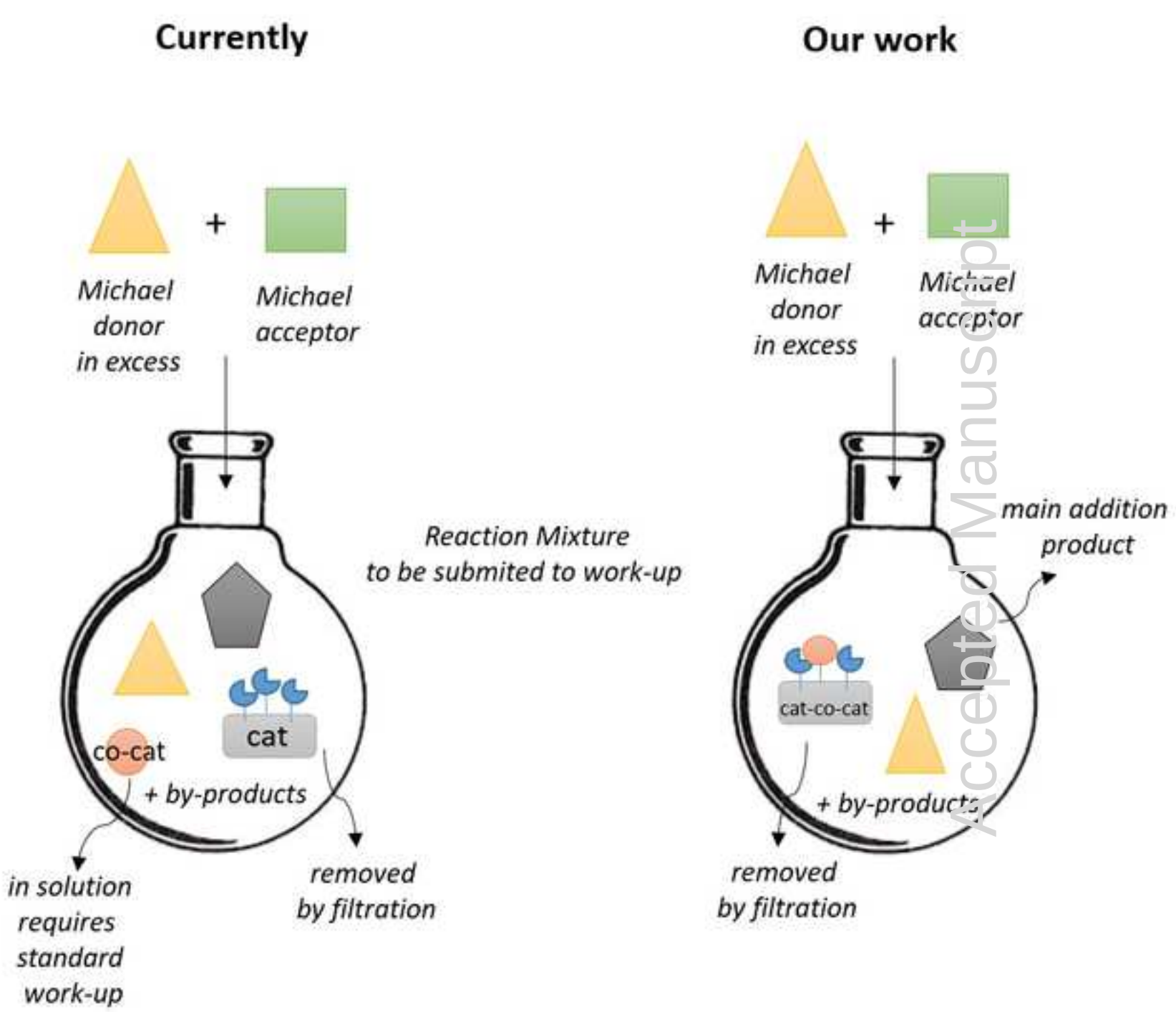

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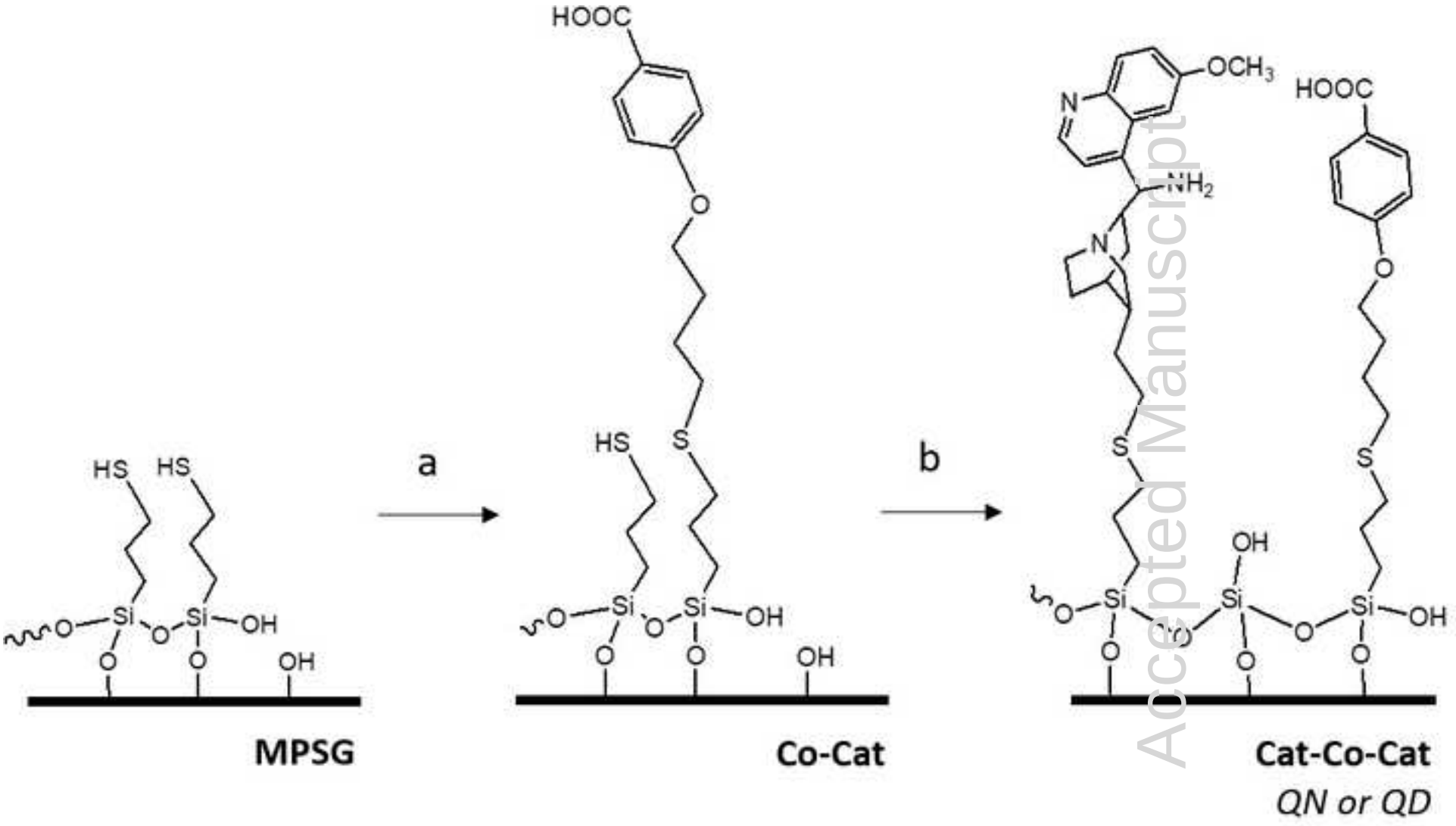

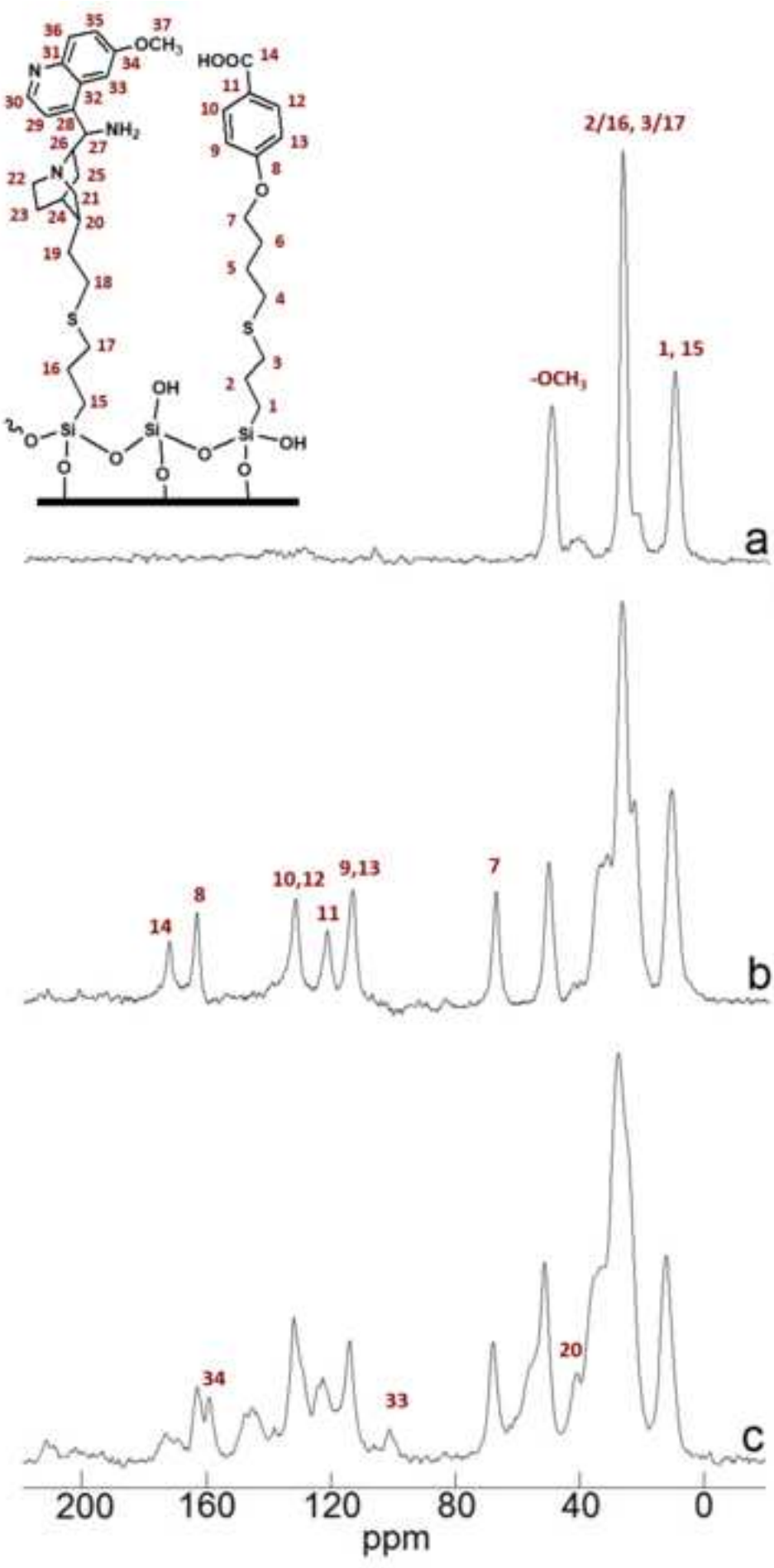

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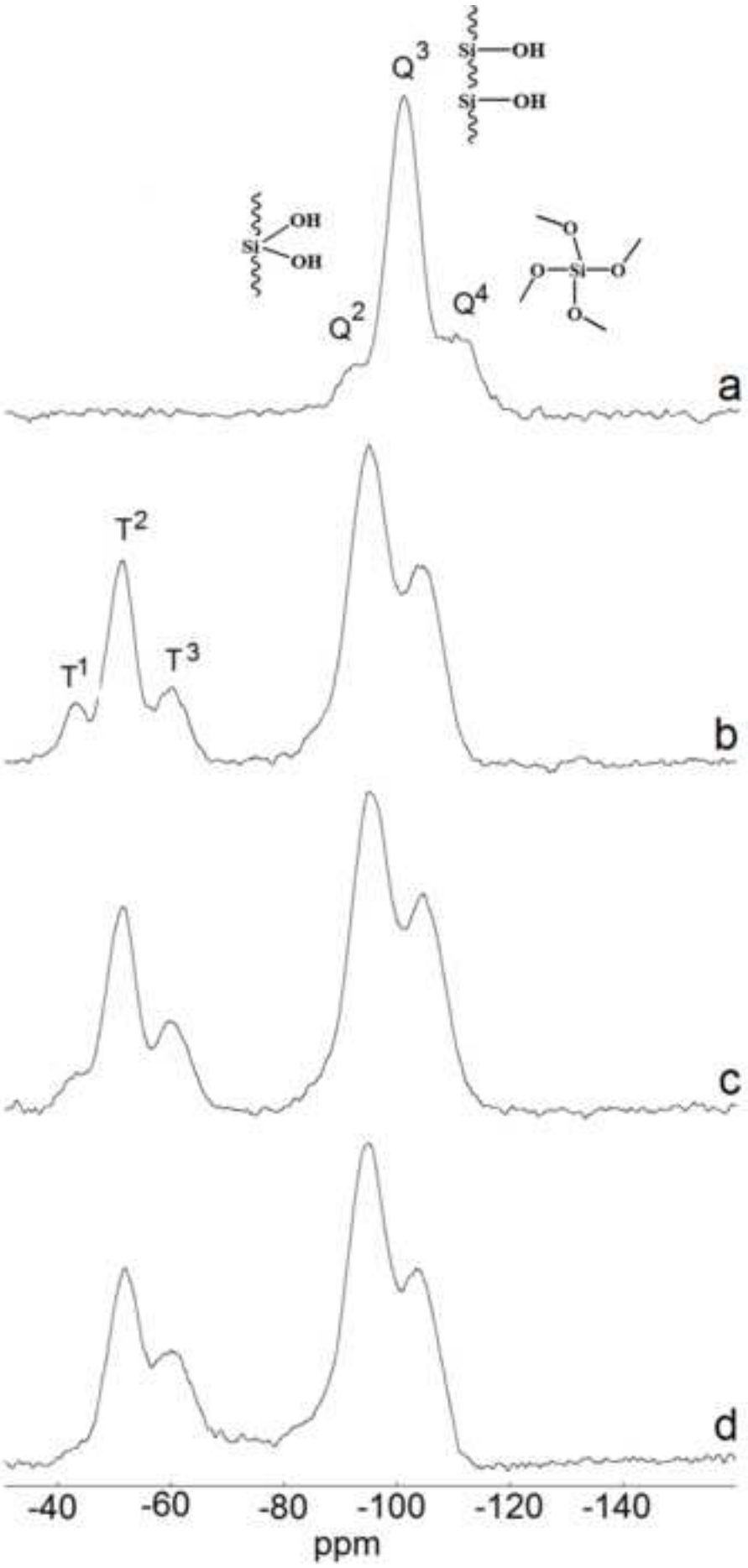

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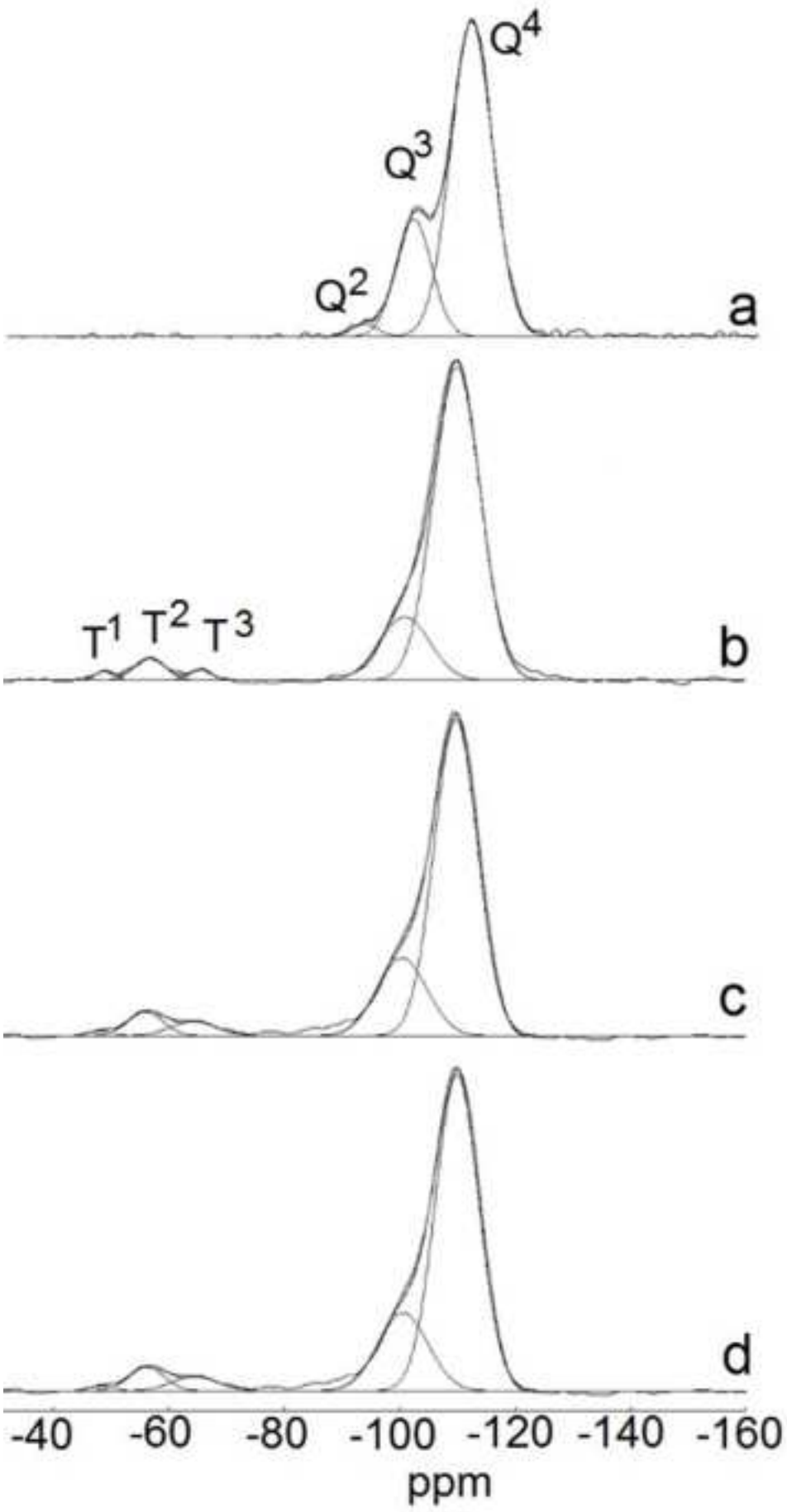

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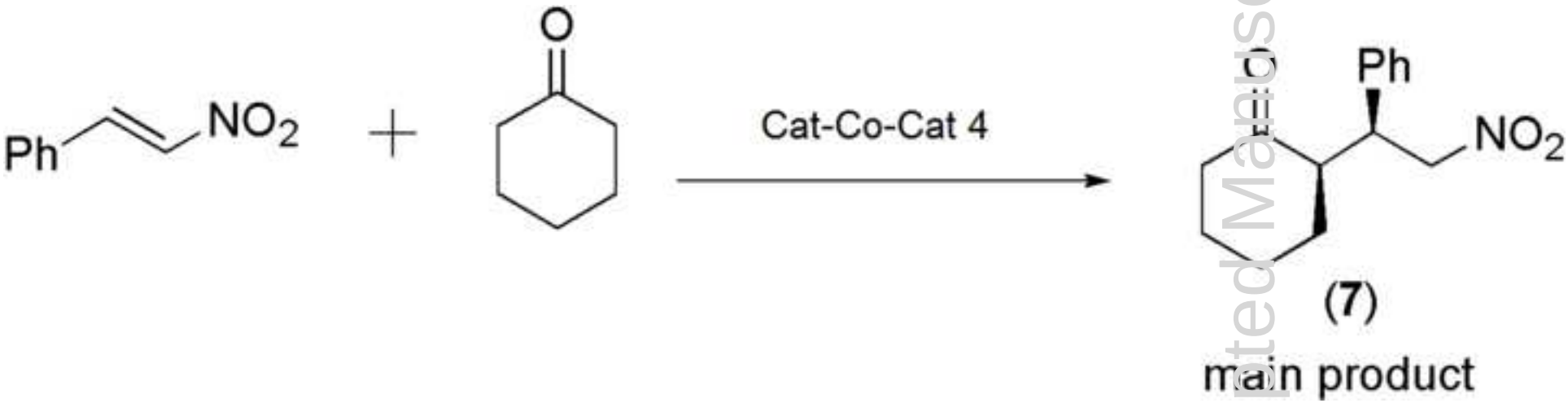

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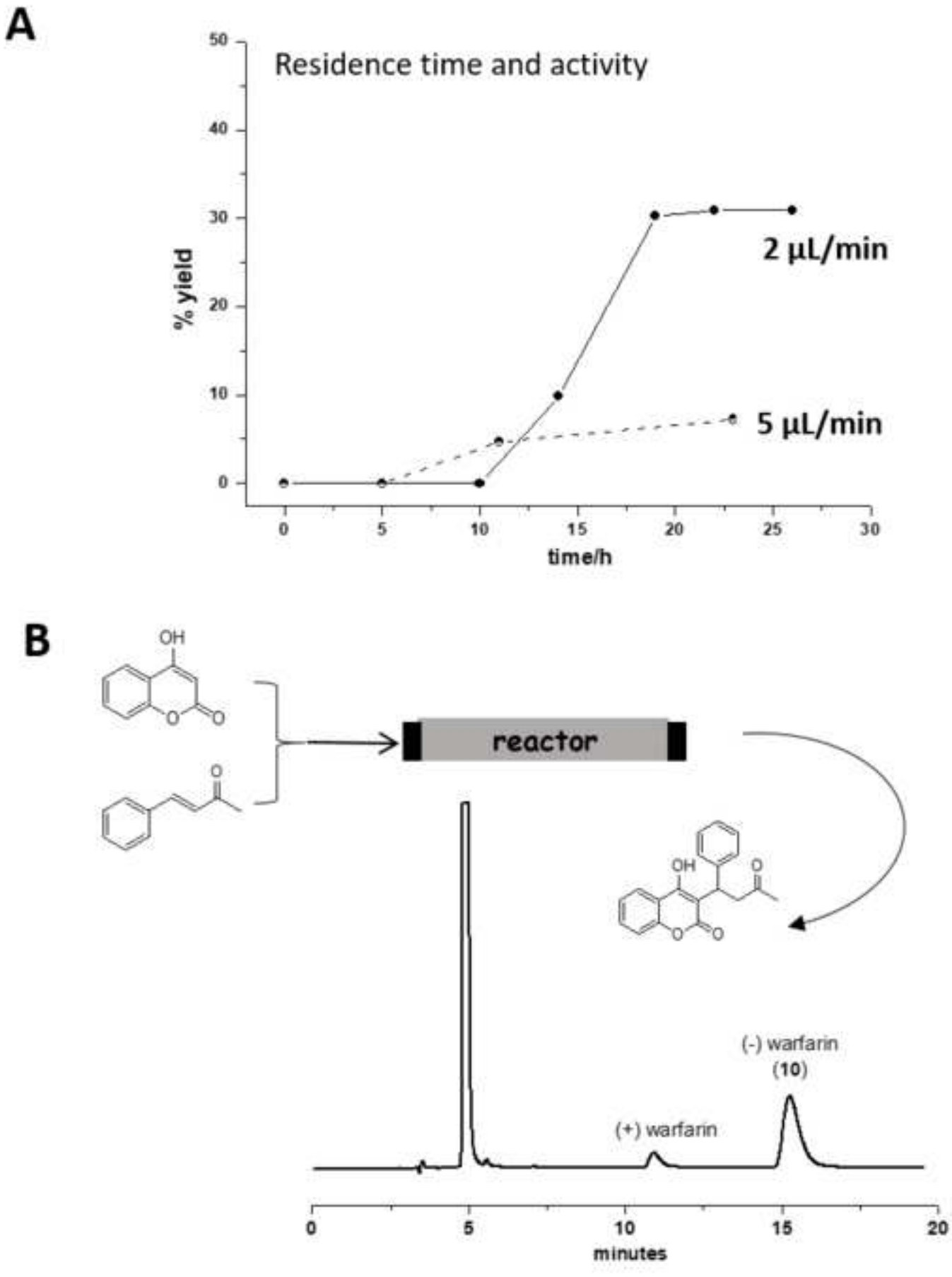

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