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Cinchona derivatives as sustainable and recyclable homogeneous organocatalysts for aza-*Markovnikov* addition

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Three cinchona derivatives have shown remarkable activity to catalyze the aza-*Markovnikov* addition reaction of *N*-heterocycles to vinyl esters. The synthesis of the aza-*Markovnikov* adducts possessing valuable biological activity was thoroughly optimized. Studying the ratio of the starting materials, bases and solvents, we achieved a new and efficient protocol, which could be performed under mild conditions with small excess of vinyl ester obtaining products with excellent yields and high regioselectivity. This optimization reduced *Sheldon*'s E-factor of the reaction by 42%. Furthermore, membrane separation for catalyst recycling was assessed to further improve the sustainability of the synthesis.

Introduction

Catalytic transformations play an increasingly important role in organic chemistry today, both in academic laboratories and in industry. Organocatalysts, enzymes and homogeneous metal catalysts are expensive, therefore new strategies have to be developed to obtain maximum catalyst performance with regards to selectivity and turnover numbers. Membrane separation in organic media is a sustainable separation technology to achieve these goals, along with process intensification and a cleaner product stream.

Cinchona alkaloids, originally isolated from the bark of Cinchona trees, are amongst the most well-known natural products with exceptional medical history and their derivatives have emerged as powerful organocatalysts, which are reported in several reviews[1-4] and recently in books.[5, 6] The widespread usage of cinchona alkaloids has been attributed to their non-toxicity, ease of use, stability, cost effectiveness, recyclability, and practical utilization in industry.[7-10]

The aza-*Markovnikov* addition is a useful nitrogen–carbon bond-forming reaction, in particular for the synthesis of bioactive *N*-heterocycle derivatives. 1-(*N*-Heterocycle) alkyl esters which could be achieved by this reaction, possess valuable biological properties[11] and can act as, acaricide (A)[12, 13], antitumor drug (B),[14] (H^+–K^+)-ATPase inhibitor (C)[15] and are also used to treat gout and certain types of kidney stones (D) (see Fig. 1.).[16] Consequently, many researchers have focused on developing new methodologies for the synthesis of 1-(*N*-heterocycle) alkyl esters. However, most of the reported synthetic protocols are associated with the use of harsh chemical conditions in which bases, acids and intense heating were usually applied to promote the reaction. In many cases, the yield and selectivity are far from satisfactory due to several side reactions.

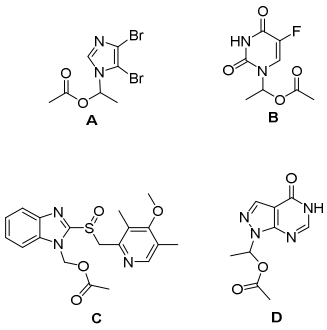

Fig. 1 Biologically active 1-(*N*-heterocycle) alkyl esters.

Many efforts have been made regarding green syntheses. In the mid-2000s, a new enzymatic strategy to perform *Markovnikov* addition was developed with the use of penicillin G acylase as catalyst.[16, 17] Later, *Lin and his co-workers* applied K_3PO_4 as a mild base,[11] and recently *Chen and his co-workers* used ionic liquids as reaction media and catalysts.[18] However, it is unsustainable to scale up this modified synthesis due to the high excess of the vinyl ester and the application of problematic solvents such as DMF.

A serious practical problem with homogeneous catalysis is the separation of reactants and products from the catalyst, which are all in the same phase. The applicability of membrane-based separation for the recovery of the homogeneous organocatalysts was explored. Membrane-based separations in organic media is a green technology that allows size-exclusion based separation of solutes in the range of 50 and 2000 g mol^{-1} by applying a pressure gradient.[19] Recent development in this field resulted in membranes, which can withstand aggressive solvents and exhibit high flux, while quasi completely rejecting relatively small solutes at the lower end

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of the nanofiltration range.[20, 21] Homogeneous catalyst recovery by membranes is an emerging field due to its mild operating conditions, low cost and easy implementation in continuous processing.[22, 23]

Here, we report a new application of cinchona alkaloids for the catalysis of aza-*Markovnikov* addition. The addition of *N*-heterocycles (imidazole, benzimidazole, pyrazole or 1,2,3-triazole) to vinyl esters (vinyl acetate or vinyl 4-*tert*-butylbenzoate) was studied and a mechanism is suggested. Our aim was to develop a new method for efficient synthesis of biologically active aza-*Markovnikov* adducts, avoiding the tedious and expensive repeated purifications and using homogeneous catalysts, which could be easily recycled after the reaction. Furthermore, our new synthesis of aza-*Markovnikov* adducts was evaluated through *Sheldon*'s E-factor.[24, 25]

Results and discussion

To turn the aza-*Markovnikov* reaction more eco-friendly, two model reactions were chosen (Scheme 1.) using *N*-heterocycles (**1** and **2**) as substrates and vinyl acetate (**3**) as a reagent resulting in two aza-*Markovnikov* adducts (**4** and **5**).

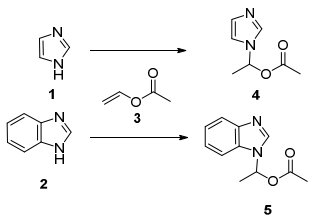
At first, it was observed that decreasing the reaction temperature (from 50 °C to 25 °C) had no significant effect on the yield of the reaction, (see Table 1., entries 1, 2 and 8, 9) and aza-*Markovnikov* addition could proceed at room temperature. Then, the influence of solvent, the molar ratio of vinyl acetate and catalyst (K_3PO_4) to *N*-heterocycle was investigated. DMF was replaced by a greener alternative,[26-28] acetonitrile (see Table 1.), providing an easier work-up process due to its lower boiling point. According to the recent critical review by *Byrne et al.*[29] about solvent selection, substitution of DMF is required, and acetonitrile is a suitable replacement. The amounts of catalyst and reagent were also decreased (see Table 1.).

The optimized process was compared to previous references by means of *Sheldon*'s E-factor. The optimization was carried out considering the load of all input materials. The results are summarized in Table 2., the E-factor for each process is expressed as the mass ratio of waste to desired aza-*Markovnikov* adduct.

As a summary of the optimization, the yields were a bit lower (in case of imidazole: from 65% to 48%, and in case of benzimidazole: from 61% to 44%). As a positive result, the decreases of E-factor calculated over the aza-*Markovnikov* addition to imidazole and benzimidazole are 42% and 30%, respectively. Therefore our results suggest, that this method is greener than the ones previously reported.[11, 30]

Three cinchona catalysts (**6–8**, see Fig. 2.) were also applied as homogeneous catalysts in aza-*Markovnikov* additions of these *N*-heterocycles to vinyl esters. Hydroquinine (**6**) is a commercially available versatile organocatalyst. The latter was converted into its amine derivative (**7**) after a mesylation, an azide formation and a catalytic hydrogenation. Amine **7** was reacted with the condensation product of 3,5-bis(trifluoromethyl)aniline and dimethyl squarate to give bifunctional cinchona-squaramide catalyst **8**.[31]

Cinchona alkaloids are well-known asymmetric catalysts giving products with high enantiomeric excesses. In the beginning of our study, we tried to prepare aza-*Markovnikov* adducts enantioselectively. According to our latest experiments, the enantiomeric excess is higher when reactions are performed at lower temperature. Therefore, the cinchona-based organocatalysts were tested and compared to the potassium phosphate first at 0 °C under the previously optimized circumstances in the aza-*Markovnikov* addition of four different *N*-heterocycles (**1**, **2**, **9**, **10**, see Table 3.) to vinyl acetate (**3**) or vinyl 4-*tert*-butylbenzoate (**11**). Mostly, the yields were lower using cinchona catalysts instead of potassium phosphate and the reactions gave racemic (ee lower than 5%) products (**4**, **5**, **12–19**, see Table 3.).



Scheme 1. Two model reactions for optimizing the aza-*Markovnikov* reaction.

Table 1. Effect of solvent and reaction conditions on the aza-*Markovnikov* addition reaction of *N*-heterocycles **1** or **2** and vinyl acetate **3** with catalyst K_3PO_4.[a,b]

Entry	Reagent	Solvent	Temperature [°C]	Equivalent of catalyst	Equivalent of vinyl ester	Yield [%][b]
1	**1**	DMF	50	0.3	8	65
2	**1**	DMF	25	0.3	8	63
3	**1**	DMF	25	0.05	8	62
4	**1**	DMF	25	0.05	1.2	52
5	**1**	MeCN	25	0.3	8	63
6	**1**	MeCN	25	0.05	8	58
7	**1**	MeCN	25	0.05	1.2	48
8	**2**	DMF	50	0.3	8	61
9	**2**	DMF	25	0.3	8	57
10	**2**	DMF	25	0.05	8	55
11	**2**	DMF	25	0.05	1.2	50
12	**2**	MeCN	25	0.3	8	60
13	**2**	MeCN	25	0.05	8	55
14	**2**	MeCN	25	0.05	1.2	44

[a]The aza-*Markovnikov* addition reaction of *N*-heterocycle **1** or **2** (0.6 mmol) and vinyl acetate **3**, with catalyst K_3PO_4 in 1.2 mL of solvent after 48 h. [b]Isolated yield of purified material.

Table 2. Effect of different methods on the *Sheldon*'s E-factor of aza-*Markovnikov* addition reaction of *N*-heterocycle **1** or **2** and vinyl acetate **3**.

Entry	Reagent	E-factor[a]	Reference
1	**1**	2.51	[11]
2	**1**	3.05	[30]
3	**1**	1.46	our work
4	**2**	2.26	[11]
5	**2**	2.52	[30]
6	**2**	1.58	our work

[a]To achieve meaningful comparisons of the different processes, solvent is generally excluded from the E-factor calculation. It was not possible to include the materials used for chromatographic purification in this comparison, since amounts of those materials are never reported in journal articles.

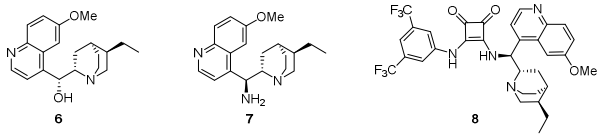
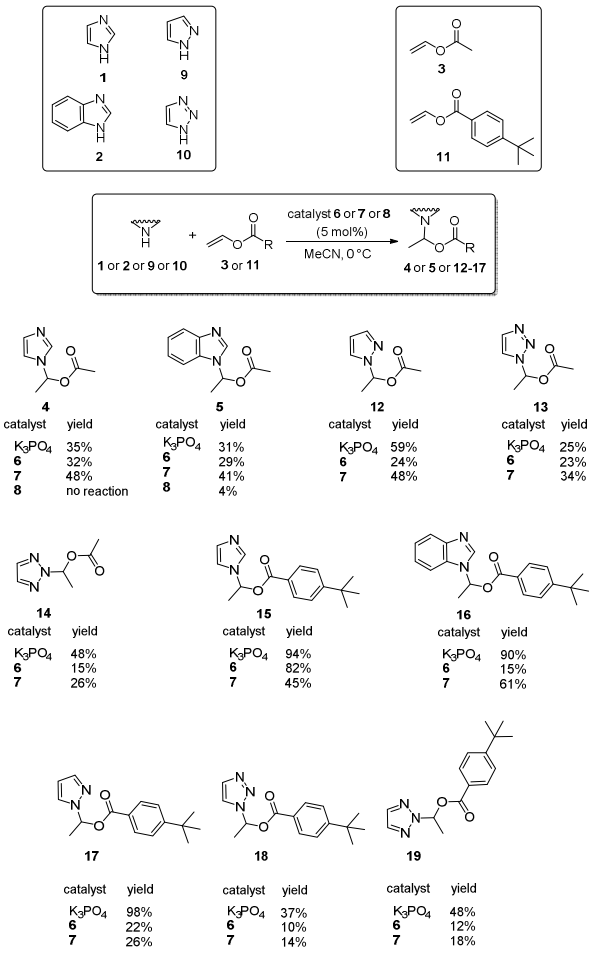


Fig. 2. Schematics of the applied cinchona organocatalysts **6**–**8**.

The results suggest, that the acyloyl part of the reagent has no influence on the reactivity: there was no significant difference between the aliphatic and aromatic reagents. Using cinchona catalysts **6**–**8** we achieved better yields only in case of reactions with imidazole (**1**) and benzimidazole (**2**). Hence, we continued the optimization using *N*-heterocycles **1** and **2** and vinyl acetate (**3**) at elevated temperature to produce aza-*Markovnikov* adducts **4** and **5** with higher yields.

Finally, cinchona-based organocatalysts **6**–**8** were applied at 25 °C and 50 °C, and the results were compared to those of obtained using potassium phosphate. As the results show in Table 4., applying cinchona amine **7** we obtained the aza-*Markovnikov* adducts with two times higher yields, than in the case of using potassium phosphate. Consequently, based on our experimental results, aza-*Markovnikov* reaction can be most environmentally friendly

Table 3. Catalytic aza-*Markovnikov* addition reaction of various *N*-heterocycles (**1** or **2** or **9** or **10**) and vinyl esters (**3** or **11**) under optimized conditions.[a,b,c,d]



[a]The aza-*Markovnikov* addition reaction of various *N*-heterocycles **1** or **2** or **9** or **10** (0.6 mmol) and vinyl esters **3** or **11** (0.72 mmol, 1.2 eq.), with catalysts K_3PO_4 or **6** or **7** or **8**, in 1.2 mL of acetonitrile at 0 °C. [b]Isolated yield of purified material. [c]After unsuccessful results were observed in case of products **4** and **5**, catalyst **8** was not applied in the other reactions. [d]Starting from vinyl acetate (**3**) or vinyl 4-*tert*-butylbenzoate (**11**), and 1,2,3-triazole (**10**) two products (**13** and **14**) or (**16** and **17**) formed in about 1:1 ratio.

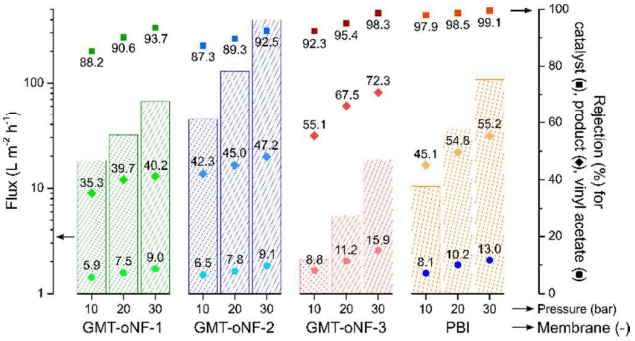


Fig. 3. Separation performance of the nanofiltration membranes in acetonitrile at 10–30 bar pressure.

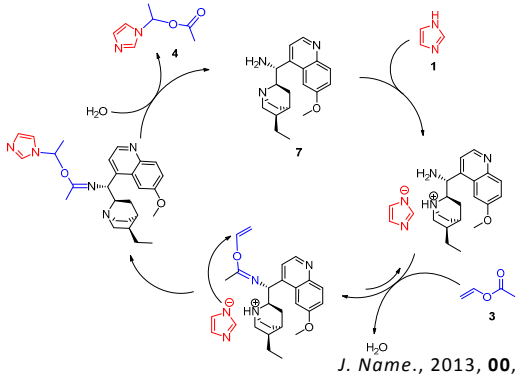
Table 4. Catalytic aza-*Markovnikov* addition reaction of *N*-heterocycles (**1** or **2**) and vinyl acetate (**3**) at different temperatures.[a]

*Yields (%) of **4** at:*	Catalyst			
	K_3PO_4	**6**	**7**	**8**
0 °C	35	32	48	0
25 °C	48	35	95	0
50 °C	91	57	98	77

*Yields (%) of **5** at:*	Catalyst			
	K_3PO_4	**6**	**7**	**8**
0 °C	31	29	41	4
25 °C	44	39	92	4
50 °C	89	60	96	74

[a]The aza-*Markovnikov* addition reaction of *N*-heterocycles 1 or 2 (0.6 mmol) and vinyl acetate 3, with catalysts K_3PO_4 or cinchona catalysts 6–8 in 1.2 mL of acetonitrile at different temperatures for 48 h.

performed at 25 °C, using acetonitrile as a solvent, and 5 mol% of cinchona amine **7**. The high yield obtained by using cinchona amine **7**, can be attributed to mechanistic reasons. The above experimental results, in accordance with the literature[32] suggest a mechanism for the aza-*Markovnikov* addition reaction catalyzed by cinchona amine **7** as achieved in Scheme 2. In a similar manner as aminocatalysis,[33] first the quinuclidine nitrogen of the cinchona amine **7** deprotonates the imidazole, then the primary amino group of cinchona amine **7** forms an enamine-type intermediate with vinyl acetate (**3**). After that, the non-bonding electron pair of the deprotonated imidazole attacks the electron poor carbon atom of



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Scheme 2. Suggested mechanism for aza-*Markovnikov* reaction using cinchona amine **7** as a catalyst.

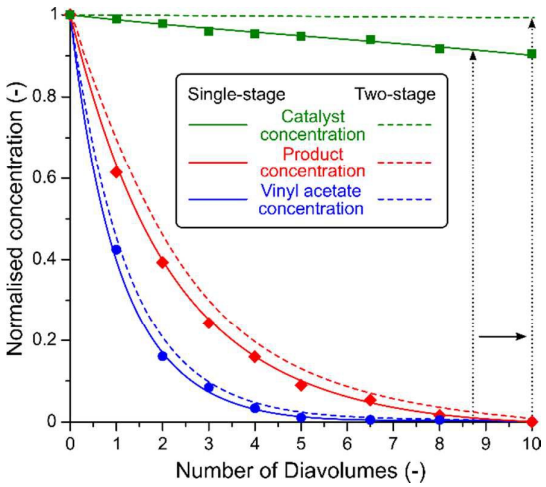

Fig. 4. Purification performance for single-stage and two-stage diafiltration processes using the PBI membrane in acetonitrile. Solid and dashed lines represent the simulated performance based on rejections, while symbols signify experimental points to validate the model used for the simulation. Dotted lines indicate 99% product removal from the system, which requires about 8.7 and 10 diavolumes for single-stage and two-stage diafiltration, respectively.

vinyl acetate (**3**). Finally, with the elimination of the product (**4**) the starting cinchona amine **7** is recovered.

Organic solvent nanofiltration (OSN) for recycling the cinchona catalysts **6–8** was explored. Commercial GMT-oNF and in-house fabricated PBI (poly[2,2'-(*m*-phenylene)-5,5'-bisbenzimidazole]) membranes were screened in acetonitrile at 10–30 bar pressure to determine their separation potential (Fig. 3.). Efficient catalyst recovery requires as high catalyst rejection as possible, ideally 100%. GMT-oNF-3 and PBI membranes at 30 bar showed the highest catalyst rejection of 98.3% and 99.1%, respectively. The latter membrane was selected for the purification process because of the lower product rejection (17%) compared to GMT-oNF-3. The rejection of the vinyl acetate (**3**), resulting from the 0.2 molar excess, was found to be as low as 13%, which allows rapid purge from the system.

The single stage diafiltration allowed 99% product removal in 8.7 diavolumes at the cost of 8% catalyst lost (Fig. 4.). The simplified membrane cascade developed by *Kim et al*. offers a sustainable approach to improve the catalyst recovery.[34] Application of their process configuration resulted in a two-stage diafiltration cascade that requires about 10 diavolumes to obtain 99% product removal and at the same time the catalyst loss can be kept as low as 1% (Fig. 4.). The purity of recycled cinchona catalyst **7** was confirmed by NMR, which confirmed that these catalysts do not degrade under the mild conditions applied during these reactions. The sustainability of the diafiltration can be further improved by *in situ* solvent recovery as recently demonstrated by *Szekely et al*.[35, 36]

Conclusions

In summary, a series of reported (**4**, **5**, **12**) and novel (**13–19**) 1-(*N*-heterocycle) alkyl esters were synthesized and characterized. The aza-*Markovnikov* reactions were performed environmentally friendly at room temperature, replacing the undesirable dimethyl formamide by acetonitrile, and decreasing the amount of the catalyst (from 30% to 5%) and the vinyl ester (from 8 equivalent to 1.2 equivalent). The reductions of *Sheldon*'s E-factor calculated for the aza-*Markovnikov* addition to imidazole and benzimidazole were 42%, and 30%, respectively.

Cinchona-based organocatalysts were synthesized and successfully applied in aza-*Markovnikov* addition as homogeneous catalysts. Using cinchona amine **7** as a catalyst, we obtained more than twice as high yield (92–95%) as using potassium phosphate. In the former case a reaction mechanism was suggested.

The homogeneous catalytic implementation of the aza-*Markovnikov* addition made this reaction more environmentally friendly by using OSN as its work up process. Due to the OSN technique, the applied catalysts were quasi completely recycled from the reaction mixture. The feasibility of membrane-based separation for catalyst recovery was demonstrated with a potential to keep the catalyst loss below 1% using a two-stage cascade configuration.

Experimental - Materials

GMT-oNF-1, GMT-oNF-2 and GMT-oNF-3 membranes were purchased from Borsig Membrane Technology GmbH (Germany). 26 wt% polybenzimidazole dissolved in *N*,*N*-dimethylacetamide (DMAc) was purchased from PBI Performance Products Inc. (USA). Non-woven polypropylene fabric Novatexx 2471 was obtained from Freudenberg Filtration Technologies (Germany).

Experimental - Membrane screening and diafiltration

The polybenzimidazole (PBI) membrane was prepared from a 26 wt% dope solution on a non-woven support sheet using a casting knife set to a thickness of 100 µm at a temperature of 20 °C based on literature procedure.[37] The feed solution for the membrane screening comprised of a mixture of catalyst, product, and substrate each of them in 0.1 g L^{-1} concentration in acetonitrile. The pressure range for the screening was 10–30 bar and the tests were carried out in across-flow nanofiltration rig (Fig. 5.). The feed solution was recirculated for 24 h followed by collection of samples from the permeate and the retentate streams. By definition, the rejection of a solute is the relative concentration decrease between the two sides of the membrane (Eq. 1.):

$$R_i = 100\% \cdot \left(1 - \frac{C_{P,i}}{C_{R,i}}\right) \quad \text{Eq. 1}$$

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where R_i is the rejection of the solute in percentage, $C_{R,i}$ and $C_{P,i}$ are the concentrations of the solute in the retentate and permeate, respectively, usually given in g L^{-1}. Flux is defined as volume of solvent that permeates the membrane per unit area in a given time (Eq. 2.):

$$F = \frac{V_P}{A\,t} \qquad \text{Eq. 2}$$

where F is the solvent flux, VP is the permeate volume, A is the membrane area and t is the time of permeation. The diafiltration was carried out by collecting the permeate separately and keeping the retentate volume constant.

Experimental - Preparation of organocatalysts and aza-*Markovnikov* reactions

General

Infrared spectra were recorded on a Bruker Alpha-T FT-IR spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. NMR spectra were recorded in $CDCl_3$ either on a Bruker DRX-500 Avance spectrometer (at 300 or 500 MHz for ^1H and at 75.5 or 125 MHz for ^{13}C spectra). Mass spectra were recorded on CAMAG TLC-MS Interface (HPLC pump: Shimadzu LC-20AD Prominence SQ MS: Shimadzu LCMS-2020 MS settings: Detector

Voltage: 1.10 kV, m/z: 105–1000, Scan speed: 1075 u/sec, DL temperature: 250 °C, Nebulizing Gas Flow: 1.5 L/min, Drying Gas

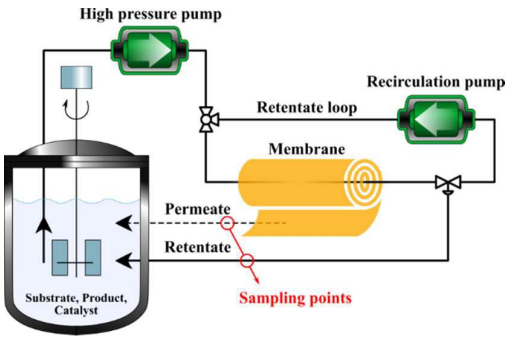

Fig. 5. Schematic of the experimental set-up for cross-flow membrane filtration.

Flow: 15 L/min. eluent: acetonitrile: 0.1 v/v% formic acid 95:5, 1.500 mL/min). Elemental analyses were performed on a Vario EL III instrument (Element analyze Corp., Germany) in the Microanalytical Laboratory of the Department of Organic Chemistry, Institute for Chemistry, L. Eötvös University, Budapest, Hungary. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) plates were used for TLC. Silica gel 60 (70–230 mesh, Merck) was used for column chromatography. Ratios of solvents for the eluents are given in volumes (mL/mL). Evaporations were carried out under reduced pressure unless otherwise stated. The cinchona-based organocatalysts (**7** and **8**) were synthesized based on the experiments of *Bae and co-workers*.[25]

General procedure for the aza-*Markovnikov* additions

Vinyl ester (0.72 mmol, 1.2 eq.) was added to a solution of the catalyst (0.03 mmol, 0.05 eq.) and *N*-heterocycle (0.6 mmol) in solvent (1.2 mL, see Table 1.). The reaction mixture was stirred at room temperature while monitored by TLC. After two days the solvent was removed. The crude product was purified by preparative thin layer chromatography on silica gel to obtain the aza-*Markovnikov* adduct as a pale yellow oil (yields can be seen in Tables 1., 3. and 4.).

1-(1*H*-Imidazol-1-yl)ethyl acetate (4)

Aza-*Markovnikov* adduct **4** was prepared as described in the *General procedure* starting from vinyl acetate (**3**, 66 µL, 62 mg, 0.72 mmol, 1.2 eq.), imidazole (**1**, 40.8 mg, 0.6 mmol) and catalyst (K_3PO_4 or **6** or **7**, 0.03 mmol, 0.05 eq.) in different solvents (1.2 mL) (see Table 1). The crude product was purified by preparative thin layer chromatography on silica gel using dichloromethane:methanol (10:1) mixture as an eluent to give aza-*Markovnikov* adduct **4** as a pale yellow oil (yields can be seen in Tables 1., 3. and 4.). Product **4** so obtained had the same spectroscopic data than those of reported.[38]

1-(1*H*-Benzo[*d*]imidazol-1-yl)ethyl acetate (5)

Aza-*Markovnikov* adduct **5** was prepared as described above in the *General procedure* starting from vinyl acetate (**3**, 66 µL, 62 mg, 0.72 mmol, 1.2 eq.), benzimidazole (**2**, 70.9 mg, 0.6 mmol) and catalyst (K_3PO_4 or **6** or **7** or **8**, 0.03 mmol, 0.05 eq.) in different solvents (1.2 mL, see Table 1.). The crude product was purified by preparative thin layer chromatography on silica gel using dichloromethane:methanol (10:1) mixture as an eluent to give aza-*Markovnikov* adduct **5** as a pale yellow oil (yields can be seen in Tables 1., 3. and 4.). Product **5** so obtained had the same spectroscopic data than those of reported.[38]

1-(1*H*-Pyrazol-1-yl)ethyl acetate (12)

Aza-*Markovnikov* adduct **12** was prepared as described above in the *General procedure* starting from vinyl acetate (**3**, 66 µL, 62 mg, 0.72 mmol, 1.2 eq.), pyrazole (**9**, 40.8 mg, 0.6 mmol) and catalyst (K_3PO_4 or **6** or **7**, 0.03 mmol, 0.05 eq.) in acetonitrile (1.2 mL). The crude product was purified by preparative thin layer chromatography on silica gel using dichloromethane:methanol (20:1) mixture as an eluent to give aza-*Markovnikov* adduct **12** as a pale yellow oil (yields can be seen in Table 3.). Product **12** so obtained had the same spectroscopic data than those of reported.[38]

1-(1*H*-1,2,3-Triazol-1-yl)ethyl acetate (13) and 1-(1*H*-1,2,3-triazol-2-yl)ethyl acetate (14)

Aza-*Markovnikov* adducts **13** and **14** were prepared as described above in the *General procedure* starting from vinyl acetate (**3**, 66 µL, 62 mg, 0.72 mmol, 1.2 eq.), 1,2,3-triazole (**10**, 41.4 mg, 0.6 mmol) and catalyst (K_3PO_4 or **6** or **7**, 0.03 mmol, 0.05 eq.) in acetonitrile

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(1.2 mL). The crude product was purified by preparative thin layer chromatography on silica gel using hexane:ethyl acetate (1:1) mixture as an eluent to give aza-*Markovnikov* adduct **13** and **14** as a pale yellow oil (yields can be seen in Table 3.). TLC (SiO_2 TLC; hexane:ethyl acetate = 1:1, R_f=0.62, UV).

1-(1*H*-1,2,3-Triazol-1-yl)ethyl acetate (13) IR (neat) ν_{max}/cm^{-1} 3132, 3002 (C=CH), 2946 (CH), 2094, 1751 (C=O), 1485, 1444, 1371, 1301, 1284, 1220, 1196, 1071. δH(500 MHz; $CDCl_3$; Me_4Si) 1.96 (3 H, d, $^3J_{H,H}$ = 6.5 Hz, CCH_3), 2.08 (3 H, s, CH_3), 7.06 (1 H, q, $J_{H,H}$ 6.5, N-CH-O), 7.71 [1 H, s, TriazC(5)-H], 7.79 [1 H, s, TriazC(4)-H]; δC(75.5 MHz; $CDCl_3$; Me_4Si) 19.64 (CH-CH_3 group), 20.79 (CH_3), 77.64 (N-CH-O), 123.43 [TriazC(5)], 133.73 [TriazC(4)], 169.39 (COO); MS (ESI): Exact mass calcd for $C_6H_9N_3O_2$: 155.16. Found *m/z* 156.200 (M^+, 56.47%). Anal. calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.26; H, 5.94; N, 27.07.

1-(1*H*-1,2,3-Triazol-2-yl)ethyl acetate (14) IR (neat) ν_{max}/cm^{-1} 3124, 3001 (C=CH), 2945 (CH), 1745 (C=O), 1447, 1414, 1370, 1344, 1214, 1117, 1079, 1064. δH(300 MHz; $CDCl_3$; Me_4Si) 1.93 (3 H, d, $J_{H,H}$ 6.5, CCH_3), 2.09 (3 H, s, CH_3), 7.15 (1 H, q, $J_{H,H}$ 6.0, N-CH-O), 7.70 [2 H, s, TriazC-H]; δC(75.5 MHz; $CDCl_3$; Me_4Si) 19.28 (CH-CH_3 group), 20.84 (CH_3), 81.25 (N-CH-O), 135.17 [TriazC], 169.12 (COO); MS (ESI): Exact mass calcd for $C_6H_9N_3O_2$: 155.16, found *m/z* 156.132 (M^+, 44.78%). Anal. calcd for $C_6H_9N_3O_2$: C, 46.45; H, 5.85; N, 27.08. Found: C, 46.26; H, 5.94; N, 27.07.

1-(1*H*-Imidazol-1-yl)ethyl 4-(*tert*-butyl)benzoate (15)

Aza-*Markovnikov* adduct **15** was prepared as described above in the *General procedure* starting from vinyl 4-(*tert*-butyl)benzoate (**11**, 147 µL, 147.1 mg, 0.72 mmol, 1.2 eq.), imidazole (**1**, 40.8 mg, 0.6 mmol) and catalyst (K_3PO_4 or **6** or **7**, 0.03 mmol, 0.05 eq.) in acetonitrile (1.2 mL). The crude product was purified by preparative thin layer chromatography on silica gel using dichloromethane:methanol (20:1) mixture as an eluent to give aza-*Markovnikov* adduct **15** as a pale yellow oil (yields can be seen in Table 3.). TLC (SiO_2 TLC; dichloromethane:methanol = 20:1, R_f=0.48, UV). IR (neat) ν_{max}/cm^{-1} 3115, 2963 (CH), 2905 (CH), 2869 (CH), 1718 (C=O), 1608 (C=C), 1493, 1261, 1223, 1188, 1071, 1033, 1014. δH(500 MHz; $CDCl_3$; Me_4Si) 1.35 (9 H, s, tBu CH_3 groups), 1.95 (3 H, d, $J_{H,H}$ 6.5, CCH_3), 6.99 (1 H, q, $J_{H,H}$ 6.0, N-CH-O), 7.10 [1 H, s, ImC(4)-H], 7.29 [1 H, s, ImC(5)-H], 7.48 and 7.95 (2×2H, AA' BB', J_{AB} 8.5, Ph-H), 7.85 [s, 1 H, ImC(2)-H]; δC(125 MHz; $CDCl_3$; Me_4Si) 20.44 (CH-CH_3 group), 31.06 (tBu CH_3 groups), 35.18 (tBu C-CH_3), 75.63 (N-CH-O), 116.85 [ImC(5)], 125.53 [PhC(3)], 126.08 [PhC(1)], 129.68 [ImC(4)], 129.74 [PhC(2)], 136.50 [ImC(2)], 157.61 [PhC(4)], 165.04 (COO); MS (ESI): Exact mass calcd for $C_{16}H_{20}N_2O_2$: 272.15, found *m/z* 273.200 (M^+, 100%). Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.48; H, 7.59; N, 10.19.

1-(1*H*-Benzo[*d*]imidazol-1-yl)ethyl 4-(*tert*-butyl)benzoate (16)

Aza-*Markovnikov* adduct **16** was prepared as described above in the *General procedure* starting from vinyl 4-(*tert*-butyl)benzoate (**11**, 147 µL, 147.1 mg, 0.72 mmol, 1.2 eq.), benzimidazole (**2**, 70.9 mg, 0.6 mmol) and catalyst (K_3PO_4 or **6** or **7**, 0.03 mmol, 0.05 eq.) in acetonitrile (1.2 mL). The crude product was purified by preparative thin layer chromatography on silica gel using dichloromethane:methanol (20:1) mixture as an eluent to give aza-*Markovnikov* adduct **16** as a pale yellow oil (yields can be seen in Table 4.). TLC (SiO_2 TLC; dichloromethane:methanol = 20:1, R_f=0.68, UV). IR (neat) ν_{max}/cm^{-1} 3058 (C=CH), 2997 (C=CH), 2963 (CH), 2869, 2748, 2720, 2684, 1938, 1726 (C=O), 1609 (C=C), 1496, 1483, 1459, 1409, 1282, 1273, 1219, 1185, 1116, 1089, 1062 δH(500 MHz; $CDCl_3$; Me_4Si) 1.34 (9 H, s, tBu CH_3 groups), 2.11 (3 H, d, $J_{H,H}$ 6.0, CCH_3), 7.30–7.37 [3 H, m, $J_{H,H}$ 6.0, N-CH-O, BimC(5)-H, BimC(6)-H], 7.46 and 7.96 (2×2H, AA' BB', J_{AB} 8.5, Ph-H), 7.70 [1 H, d, $J_{H,H}$ 8.0, BimC(4)-H or BimC(7)-H], 7.84 [1 H, s, $J_{H,H}$ 7.5, BimC(4)-H or BimC(7)-H], 8.24 [1 H, s, BimC(2)-H]; δC(125 MHz; $CDCl_3$; Me_4Si) 20.10 (CH-CH_3 group), 31.05 (tBu CH_3 groups), 35.18 (tBu C-CH_3), 75.43 (N-CH-O), 110.98 [BimC(7)], 120.62 [BimC(4)], 122.86 [BimC(5), BimC(6)], 123.62 [BimC(5), BimC(6)], 125.55 [PhC(3)], 126.00 [PhC(1)], 129.77 [PhC(2)], 132.47 [Bim(8)], 141.13 [Bim(9)], 143.97 [Bim(2)], 157.62 [PhC(4)], 165.08 (COO); MS (ESI): Exact mass calcd for $C_{20}H_{22}N_2O_2$: 322.17, found *m/z* 323.200 (M^+, 100%). Anal. calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.49; H, 6.90; N, 8.68.

1-(1*H*-Pyrazol-1-yl)ethyl 4-(*tert*-butyl)benzoate (17)

Aza-*Markovnikov* adduct **17** was prepared as described above in the *General procedure* starting from vinyl 4-(*tert*-butyl)benzoate (**11**, 147 µL, 147.1 mg, 0.72 mmol, 1.2 eq.), pyrazole (**9**, 40.8 mg, 0.6 mmol) and catalyst (K_3PO_4 or **6** or **7**, 0.03 mmol, 0.05 eq.) in acetonitrile (1.2 mL). The crude product was purified by preparative thin layer chromatography on silica gel using hexane:ethyl acetate (4:1) mixture as an eluent to give aza-*Markovnikov* adduct **17** as a pale yellow oil (yields can be seen in Table 3.). TLC (SiO_2 TLC; hexane:ethyl acetate = 4:1, R_f=0.41, UV). IR (neat) ν_{max}/cm^{-1} 3122, 2964 (CH), 2906 (CH), 2870 (CH), 2427, 2296, 2097, 1931, 1806, 1719 (C=O), 1609 (C=C), 1519, 1441, 1398, 1256, 1188, 1113, 1089, 1066, 1041, 1014. δH(500 MHz; $CDCl_3$; Me_4Si) 1.34 (9 H, s, tBu CH_3 groups), 2.02 (3 H, d, $J_{H,H}$ 6.5, CCH_3), 6.31 [1 H, t, $J_{H,H}$ 2.0, PyrC(4)], 7.10 (1 H, q, $J_{H,H}$ 6.0, N-CH-O), 7.45 and 7.98 (2×2H, AA'BB', J_{AB} 8.5, Ph-H), 7.62 [1 H, s, PyrC(3)-H], 7.75 [1 H, d, $J_{H,H}$ 2.5, PyrC(5)-H]; δC(125 MHz; $CDCl_3$; Me_4Si) 19.42 (CH-CH_3 group), 31.07 (tBu CH_3 groups), 35.13 (tBu C-CH_3), 79.24 (N-CH-O), 106.15 [PyrC(4)], 125.40 [PhC(3)], 126.46 [PhC(1)], 129.81 [PhC(2)], 129.87 [PyrC(5)], 140.46 [PyrC(3)], 157.30 [PhC(4)], 165.35 (COO); MS (ESI): Exact mass calcd for $C_{16}H_{20}N_2O_2$: 272.15, found *m/z* 273.200 (M^+, 100%). Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.49; H, 7.45; N, 10.23.

1-(1*H*-Triazol-1-yl)ethyl 4-(*tert*-butyl)benzoate (18) and 1-(1*H*-triazol-2-yl)ethyl 4-(*tert*-butyl)benzoate (19)

Aza-*Markovnikov* adducts **18** and **19** were prepared as described above in the *General procedure* starting from vinyl 4-(*tert*-butyl)benzoate (**11**, 147 µL, 147.1 mg, 0.72 mmol, 1.2 eq.), 1,2,3-

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triazole (**10**, 41.4 mg, 0.6 mmol) and catalyst (K_3PO_4 or **6** or **7**, 0.03 mmol, 0.05 eq.) in acetonitrile (1.2 mL). The crude product was purified by preparative thin layer chromatography on silica gel using hexane:ethyl acetate (1:1) mixture as an eluent to give aza-*Markovnikov* adduct **18** and **19** as a pale yellow oil (yields can be seen in Table 3.).

1-(1*H*-Triazol-1-yl)ethyl 4-(*tert*-butyl)benzoate (18) TLC (SiO_2 TLC; hexane:ethyl acetate = 1:1, R_f=0.48, UV). IR (neat) ν_{max}/cm^{-1} 3130, 2963 (CH), 2870 (CH), 2389, 2300, 2096, 1938, 1719 (C=O), 1608 (C=C), 1573, 1460, 1409, 1365, 1339, 1262, 1187, 1078, 1034, 1011. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.34 (9 H, s, tBu CH_3 groups), 2.13 (3 H, d, $J_{H,H}$ 6.5, CCH_3), 7.32 (1 H, q, $J_{H,H}$ 6.5, N-CH-O), 7.48 and 7.98 (2×2H, AA'BB', J_{AB} 8.5, Ph-H), 7.74 [1 H, s, TriazC(5)-H], 7.90 [1 H, s, TriazC(4)-H]; δC(125 MHz; $CDCl_3$; Me_4Si) 19.69 (CH-CH_3 group), 31.04 (tBu CH_3 groups), 35.20 (tBu C-CH_3), 77.98 (N-CH-O), 125.58 [PhC(3)],123.63 [TriazC(3)], 126.19 [PhC(1)], 129.89 [PhC(2)], 135.15 [TriazC(4)], 157.86 [PhC(4)], 164.95 (COO); MS (ESI): Exact mass calcd for $C_{15}H_{19}N_3O_2$: 273.15, found *m/z* 274.100 (M^+, 177.43%). Anal. calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.82; H, 7.18; N, 15.35.

1-(1*H*-1,2,3-Triazol-2-yl)ethyl 4-(*tert*-butyl)benzoate (19) TLC (SiO_2 TLC; hexane:ethyl acetate = 1:1, R_f=0.82, UV). IR (neat) ν_{max}/cm^{-1} 3428, 2964 (CH), 2869 (CH), 2399, 2281, 2098, 1939, 1724 (C=O), 1609 (C=C), 1572, 1463, 1410, 1365, 1343, 1267, 1242, 1188, 1089, 1061, 1015. δH(500 MHz; $CDCl_3$; Me_4Si) 1.33 (9 H, s, tBu CH_3 groups), 2.06 (3 H, d, $J_{H,H}$ 6.5, CCH_3), 7.42–7.44 [1 H, m, N-CH-O], 7.44 and 7.98 (2×2H, AA'BB', J_{AB} 8.5, Ph-H), 7.72 [2 H, s, TriazC(4)-H, TriazC(5)-H]; δC(125 MHz; $CDCl_3$; Me_4Si) 19.38 (CH-CH_3 group), 31.06 (tBu CH_3 groups), 35.14 (tBu C-CH_3), 81.46 (N-CH-O), 125.42 [PhC(3)], 126.19 [PhC(1)], 129.90 [PhC(2)], 135.15 [TriazC(4), TriazC(5)], 157.38 [PhC(4)], 164.67 (COO); MS (ESI): Exact mass calcd for $C_{15}H_{19}N_3O_2$: 273.15, found *m/z* 274.200 (M^+, 91.42%). Anal. calcd for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37. Found: C, 65.79; H, 7.20; N, 15.34.

Conflicts of interest

There are no conflicts to declare.

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Cinchona derivatives as sustainable and recyclable homogeneous organocatalysts for aza-*Markovnikov* addition.

Sándor Nagy, Zsuzsanna Fehér, Péter Kisszékelyi, Péter Huszthy and József Kupai

Aza-*Markovnikov* additions were achieved with up to 98% yields using cinchona based organocatalysts that were recycled by organic solvent nanofiltration.