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Primary Amine Attached to an *N*-(Carboxyalkyl)imidazolium Cation: A Recyclable Organocatalyst for the Asymmetric Michael Reaction

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A (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine derivative modified with an *N*-(4-carboxybutyl)imidazolium cation and PF_6^- anion has been developed and applied as a recyclable organocatalyst of the asymmetric 1,4-conjugate addition of 4-hydroxy-2*H*-chromen-2-one to 1-substituted buten-3-ones or cyclohexen-3-one to afford corresponding Michael adducts in high yields (up to 97 %) and enantioselectivities (up to 90 % *ee*). The most active (*S*) enantiomer of the clinically useful anticoagulant warfarin was prepared in this way. The catalyst exhibited better recyclability than its known analog, which does not contain a carboxy group: it could be recycled 5 times in the reaction without a significant decrease in product yield or *ee* values. Gradual deactivation of the catalyst was caused by leaching during workup rather than by off-cycle reactions between the catalyst and reagents.

Introduction

Asymmetric organocatalysis is an intensively evolving area of modern organic chemistry.[1] It allows enantioselective synthesis of complex organic molecules from available prochiral precursors by using metal-free organocatalysts, in particular of natural origin, and rather simple experimental procedures.[2] However, in spite of impressive results obtained over recent years, just a few applications of organocatalysis in the pharmaceutical sector have been reported so far,[3] which may be attributed to difficulties of product isolation (chromatography) and chiral catalyst recovery.

To address these issues, recyclable versions of organocatalysts tagged to polymers[4] or ionic groups[5] have been designed. Supported organocatalysts are easily separated from the products formed owing to their different solubility in organic solvents or sometimes water. However, catalyst samples recycled several times commonly became less active owing to leaching and/or poisoning by off-cycle by-products.[6] As a rule, supported α-amino acids[7] and proline/glutamine-derived di- or tri-peptides[8] with a terminal carboxylic group exhibit better sustainability. Evidently, the carboxylic group inhibits undesirable side-reactions that destroy the catalyst and reduces the lipophilicity of the molecule minimizing its loss during the product extraction.[9] Yet, α-amino acids, in particular proline derivatives, which are efficient catalysts of asymmetric aldol reactions,[10] appeared less efficient in asymmetric Michael reactions in which nucleophilicity and in some cases steric accessibility of the catalyst active site play an important role.[11] Indeed, asymmetric conjugate additions of 4-hydroxycoumarin to α,β-unsaturated ketones used for the enantioselective synthesis of clinically useful medications (particularly, of the anticoagulant warfarin[12]), proceed faster and more selectively in the presence of chiral primary amines[13] or diamines[14] than in the presence of amino acid derived organocatalysts.[15]

For these reactions we have recently synthesized (1*S*,2*S*)-1,2-diaminodiphenylethane-based catalyst **1** modified with the *N*-methylimidazolium cation and the PF_6^- anion.[16] The catalyst exhibited reasonable activity and enantioselectivity of the reaction between 4-hydroxycoumarin and benzylideneacetone in the first 3 cycles; although afterwards catalytic efficacy progressively declined. A plausible reason for the deactivation was the irreversible formation of cyclic compound **2** between the catalyst and the Michael adduct (this is supported by MS data). The treatment of a trice-recycled sample of catalyst **1** with AcOH cleaved this by-product and for a while restored activity of the catalyst (Figure 1).

We supposed that the carboxylic group introduced directly into the supported catalyst (e.g. into the cation unit) would suppress Brønsted acid sensitive off-cycle transformations during the catalytic reactions. We expected that such modification of the molecule periphery would exert

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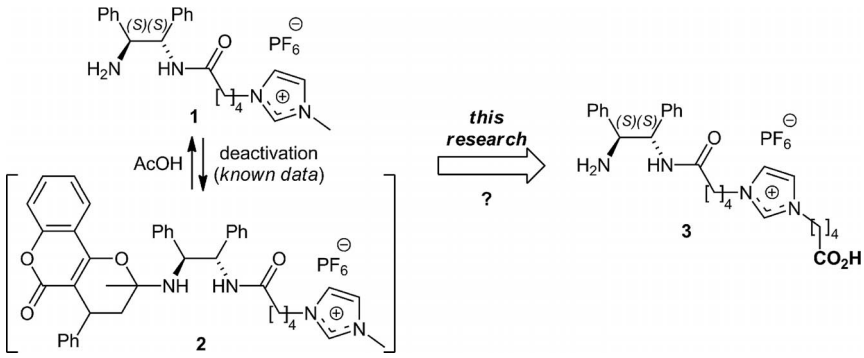


Figure 1. Strategy of the research.

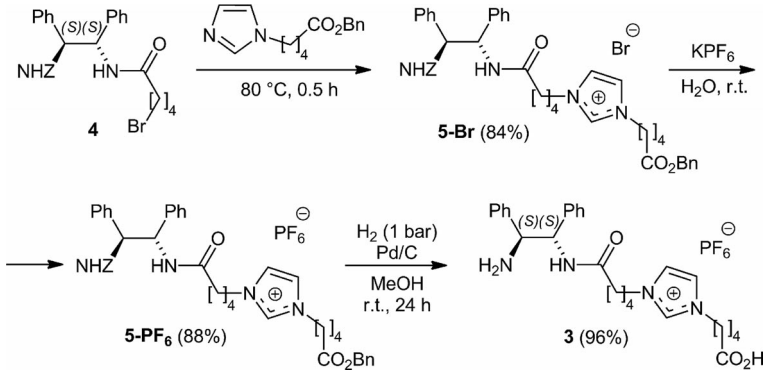
no negative impact on the activity and/or stereoinduction capability of resulting catalyst **3**, but would slow down the undesirable processes that poison the catalyst.

Results and Discussion

To verify our hypothesis we synthesized (1*S*,2*S*)-1,2-diaminodiphenylethane derivative **3** modified with an *N*-(4-carboxybutyl)imidazolium cation and a PF_6^- anion through *N*-alkylation of benzyl 5-(1*H*-imidazol-1-yl)pentanoate with pre-prepared[16] bromoamide **4** followed by metathesis of the anion in alkylation product **5-Br** and catalytic deprotection of resulting hexafluorophosphate **5-PF$_6$** to give target catalyst **3**. Each step of this sequence selectively afforded either intermediates or the final product in high yields (Scheme 1). Salt **3** melts at 105 °C and can be regarded as a chiral ionic liquid.

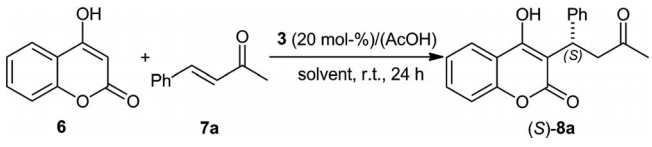
We evaluated the catalytic properties of compound **3** in an asymmetric reaction of 4-hydroxy-2*H*-chromen-2-one (**6**) with benzylideneacetone (**7a**; Table 1). The reaction ran in various solvents [tetrahydrofuran (THF), CH_2Cl_2, *i*PrOH or H_2O] in the presence of amine **3** (20 mol-%) to afford adduct **8a** with moderate enantioselectivity (62–67% *ee*), which was similar to the values attained in corresponding reactions catalyzed by carboxyl-free chiral amine **1** (Table 1, Entries 1–4). However, catalyst **3** appeared more active than catalyst **1** under the studied conditions: the yield of product **8a** in THF solution after 24 h was 96%, whereas the corresponding reaction catalyzed with amine **1** afforded compound **8a** in just 73% yield over 45 h.[16] The acidic additive (AcOH) exerted a favorable impact on enantioselectivity (Table 1, Entries 5–10). A compromise between the yield (93%) and enantiomeric purity (82% *ee*) of product **8a** was attained at ambient temperature in which 20 mol-% of **3** and 5 equiv. of AcOH with respect to **6** were used (Table 1, Entry 5). Furthermore, the *ee* value of raw product **8a** (82%) could be improved to 97% through a single crystallization from an acetone/water mixture. Variations in catalyst **3** and/or AcOH amounts did not bring about a positive effect. The product yield dropped to 60% when the reaction was carried out at +4 °C for 48 h, nevertheless, it was noticeably higher than in the presence of catalyst **1** under similar conditions (40% over 70 h; Table 1, Entry 10). According to the optical rotation sign, the major enantiomer of product **8a** had the absolute (–)-(*S*) configuration.[17] Importantly, the (*S*) enantiomer of **8a** proved to have anticoagulant activity 2–5 times higher than the corresponding (*R*) enantiomer.[18]

4-Hydroxy-2*H*-chromen-2-one **6** reacted with α,β-enones **7a**–**g** bearing aromatic, heteroaromatic, alicyclic or organometallic groups at the β-carbon atom in the presence of amino acid **3** under optimal conditions to afford corresponding Michael adducts **8a**–**g** in high yields with moderate to high enantioselectivity (Table 2, Entries 1–7). Cyclohexenone **7h** also appeared a suitable starting material, but the optical purity of product **8h** was modest (Table 2, En-



Scheme 1. Synthesis of primary amine derived organocatalyst **3** modified with an *N*-(4-carboxy-*n*-butyl)imidazolium cation and a PF_6^- anion.

Table 1. Primary amine **3** catalyzed reaction between **6** and **7a**.[a]

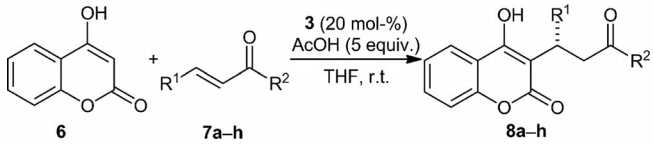


6 **7a** (*S*)-**8a**

Entry	Solvent	AcOH [equiv.]	**8a** Yield [%][b]	*ee* [%][c]
1	THF	–	96 (73[d])	67 (68[d])
2	CH_2Cl_2	–	94	62
3	*i*PrOH	–	94	63
4	H_2O	–	60	63
5	THF	5	93 (97[d])	82 (78[d])
6[e]	THF	5	98	80
7[f]	THF	5	82	78
8	THF	2.5	85	78
9	THF	10	97	80
10[g]	THF	5	60 (40[h])	83 (79[h])

[a] Unless otherwise specified, all reactions were carried out with **3** (12.2 mg, 0.02 mmol), **6** (16.2 mg, 0.10 mmol), **7a** (17.5 mg, 0.12 mmol), an appropriate solvent (0.15 mL), and AcOH (2.5–10 equiv.). [b] Isolated yield of product **8a** after column chromatography on silica gel. [c] HPLC analysis data [Chiralpak AD-H, hexane/*i*PrOH = 70:30, 0.7 mL min^{-1}, 254 nm, t_R = 5.44 min (minor), 10.90 min (major)]. The absolute configuration was determined by comparison of the optical rotation of product (*S*)-**8a** [α_D^{25} = –11.4 (*c* = 0.70, MeCN); 80% *ee*] with reported data [ref.[17] α_D^{25} = –15.5 (*c* = 3, MeCN); 99% *ee*]. [d] The reaction was carried out in the presence of catalyst **1** (20 mol-%) for 45 h.[16] [e] The reaction was carried out in the presence of 25 mol-% of catalyst **3**. [f] The reaction was carried out in the presence of 15 mol-% of catalyst **3**. [g] The reaction was carried out at +4 °C for 48 h. [h] The reaction was carried out in the presence of catalyst **1** (20 mol-%) and AcOH (10 equiv.) at +5 °C for 70 h.[16]

Table 2. Asymmetric Michael reactions of compound **6** with α,β-unsaturated ketones **7** in the presence of the **3**/AcOH catalytic system.[a]



6 **7a–h** **8a–h**

Entry	R^1, R^2	Time [h]	**8** Yield [%][b]	*ee* [%][c]
1	Ph, Me (**7a**)	24	93 (**a**)	82 (78[d])
2	4-$MeOC_6H_4$, Me (**7b**)	48	78 (**b**)	79 (77[d])
3	3-pyridyl, Me (**7c**)	36	97 (**c**)	70
4	2-thienyl, Me (**7d**)	30	85 (**d**)	71
5	*cyclo*-C_6H_{11}, Me (**7e**)	48	75 (**e**)	90
6	ferrocenyl, Me (**7f**)	48	70 (**f**)	51
7	cymantrenyl, Me (**7g**)	48	70 (**g**)	72
8	–$[CH_2]_3$– (**7h**)	48	50 (**h**)	54 (50[d])

[a] Reaction conditions: organocatalyst **3** (12.2 mg, 0.02 mmol), **6** (0.10 mmol), **7** (0.12 mmol), and AcOH (30 μL, 0.50 mmol). [b] Isolated yield of product **8** after column chromatography on silica gel. [c] HPLC analysis data (Chiralpak AD-H, hexane/*i*PrOH, 0.7 mL min^{-1}, 220 or 254 nm). [d] Data for corresponding reactions in the presence of catalyst **1** (20 mol-%) are given in parentheses.[16]

Table 3. Recycling of catalyst **3** in the reaction of **6** with **7a** in the AcOH/THF system.[a]

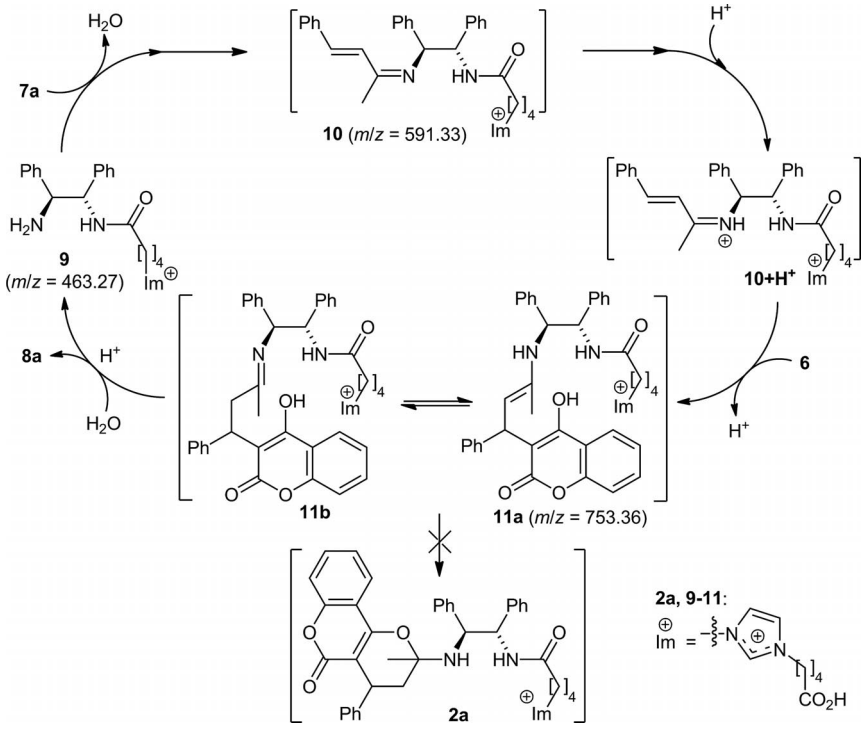
Cycle	Time [h]	**8a** Yield [%]	*ee* [%]	**3** Mass [mg]
1	24 (45)	93 (97)	82 (78)	12.2
2	24 (45)	91 (94)	82 (78)	11.8
3	24 (45)	90 (93)	81 (77)	11.2
4	24 (45)	86 (61)	80 (76)	10.1
5	24 (45)	75 (42)	79 (76)	8.6
6	24 (100)	65 (51)	77 (73)	7.3

[a] Data for corresponding reactions in the presence of recyclable catalyst **1**[16] are given in parentheses.

try 8). Adducts **7f**,**g** incorporate ferrocene or cymantrene units, which are integral parts of useful compounds with antimalarial, antitumor and other types of biological activities.[19] The proposed approach allows a simple catalytic synthesis of these new warfarin analogs.

Next, we studied the recyclability of catalyst **3** in the asymmetric Michael reaction between compounds **6** and **7a**. The reaction was stopped after 24 h, and volatile components of the system were evaporated under reduced pressure. Then, adduct **8a** was extracted with Et_2O, and fresh portions of starting compounds, AcOH and THF were added to the remaining catalyst (Table 3). As expected, amino acid **3** appeared to be a more active and robust catalyst for the studied reaction than primary amine **1**. Unlike the latter, it could be recycled 4–5 times with only a minor decrease in yield and selectivity for **8a**.

To reveal a reason for the improved catalytic performance, we recorded the mass spectra (ESI$^+$) of freshly prepared catalyst **3** and of four other catalyst samples, one of which was taken from the reaction stopped after 2 h, and the other three used in the reaction for one (24 h), two (48 h) and five (120 h) catalytic cycles, respectively. The mass spectra of starting catalyst **3** contained mainly a peak corresponding to cation **9** (*m*/*z* = 463.27; Scheme 2). The same peak also dominated the mass spectra of the recycled samples. Minor peaks of other ions participating in the catalytic cycle were only detected in the spectra of the sample that had been removed from the reaction mass after 2 h. These peaks were assigned to corresponding cations **10** (*m*/*z* = 591.33; $I \approx 15\%$) and **11** (*m*/*z* = 753.36; $I \approx 2\%$) in accordance with *m*/*z* values and their relation to the reported mechanisms of organocatalytic Michael reactions.[16,20] They were absent in the mass spectra of the samples that had operated over 24–120 h, and this fact may be attributed to rapid hydrolysis of cation **11** to product **8a** and active cation **9** promoted by acidic components of the catalytic system (the carboxylic group of **3** and AcOH). Evidently, multiply recycled catalyst **3** was not contaminated by isomeric off-cycle ion **2a**, which is an analogue of cation **2** that poisoned similar catalyst **1** in the long run (when it was used more than thrice;[16] Figure 1). A steady decrease in the yield and, to some extent, the *ee* value of product **8a** in each next cycle may be caused by a reduction of the mass of catalyst **3** owing to its gradual leaching into organic solution during workup (Table 3).



Scheme 2. Transformations of cation **9** in the asymmetric Michael reaction between **6** and **7a** according to mass spectral results.

Conclusions

We have found that sustainability of ionic-liquid-supported primary-amine-derived recyclable chiral organocatalysts for asymmetric Michael reactions can be improved by the incorporation of a peripheral carboxylic group that suppresses undesirable off-cycle reactions during the catalytic process. In the presence of the new (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine derivative modified with an *N*-(4-carboxybutyl)imidazolium cation and PF_6^- anion (20 mol-%), and AcOH (5 equiv.), 4-hydroxy-2*H*-chromen-2-one reacted with 1-substituted buten-3-ones or cyclohexen-3-one to afford corresponding Michael adducts in high yields (up to 97%) and enantioselectivities (up to 90% *ee*). Unlike similar catalysts without the carboxylic group, the developed catalyst can be recycled 5 times with just a minor decrease in product yield and reaction enantioselectivity. Gradual deactivation of the catalyst was caused by leaching during workup rather than by off-cycle reactions between the catalyst and reagents (supported by mass spectral data). Hopefully, the proposed approach may be successfully employed in designing robust commercial catalytic systems for the asymmetric synthesis of biologically active compounds.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded with a Bruker AM 300 spectrometer in $CDCl_3$ and [D_6]DMSO. The chemical shifts for ^1H and ^{13}C were measured relative to Me_4Si or $CDCl_3$, respectively. HR mass spectra were measured with a Bruker micro-TOF II spectrometer by using electrospray ionization (ESI). The measurements were taken in the positive ion mode (interface capillary voltage 4500 V) in the mass range *m*/*z* = 50–3000 Da; external or internal calibration was done with an electrospray calibrant solution (Agilent). Syringe injection was used for the solution in MeCN/H_2O (flow rate 3 μL/min). Nitrogen was applied as dry gas, and the interface temperature was set at 180 °C.[21] Specific optical rotations $[\alpha]_D^{20}$ were measured with a Jasco DIP-360 instrument at 589 nm. Silica gel 0.060–0.200 (Acros) was used for column chromatography. α,β-Unsaturated ketones **7a**,[22] **7b**–**d**[23] and **7f**[24] were synthesized by known procedures. Synthesis of **7g** is described in the Supporting Information. Compounds **6** and **7h** were purchased from Aldrich and used without purification. The solvents were purified by standard procedures.

Catalyst Preparation

3-{5-[(1*S*,2*S*)-2-(Benzyloxycarbonylamino)-1,2-diphenylethylamino]-5-oxopentyl}-1-[5-(benzyloxy)-5-oxopentyl]-1*H*-imidazol-3-ium Bromide (5-Br): A mixture of benzyl (1*S*,2*S*)-2-(5-bromopentanamido)-1,2-diphenylethylcarbamate (**4**; 1.79 g, 3.52 mmol) and benzyl 5-(1*H*-imidazol-1-yl)pentanoate[25] (1.00 g, 3.87 mmol) was stirred at 80 °C for 30 min and cooled to ambient temperature. The reaction mixture was thoroughly washed with diethyl ether (5× 10 mL) and dried in vacuo (0.5 Torr) at 50 °C for 2 h to afford **5-Br** (2.00 g, 84%) as a colorless solid. M.p. 79–80 °C. $[\alpha]_D^{20}$ = +2.5 (*c* = 1, MeOH). ^1H NMR ([D_6]DMSO): δ = 9.19–9.00 (s, 1 H), 8.45 (m, 1 H), 7.90–7.71 (m, 3 H), 7.53–6.93 (m, 20 H), 5.28 (m, 1 H), 5.07 (m, 4 H), 4.93–4.89 (m, 1 H), 4.29–4.13 (m, 2 H), 4.12–3.91 (m, 2 H), 2.41–2.29 (m, 4 H), 2.09 (m, 2 H), 2.09–1.51 (m, 8 H) ppm. ^{13}C NMR ([D_6]DMSO): δ = 172.5, 171.6, 155.9, 140.4, 135.7, 127.9, 126.4–121.3 (Ar), 122.4, 65.4, 59.2, 56.6, 48.4, 39.5, 34.3, 32.6, 28.7, 24.5, 21.5, 20.9 ppm. HRMS: calcd. for $C_{42}H_{47}N_4O_5^+$ $[M]^+$ 687.3541; found 687.3549.

3-{5-[(1*S*,2*S*)-2-(Benzyloxycarbonylamino)-1,2-diphenylethylamino]-5-oxopentyl}-1-[5-(benzyloxy)-5-oxopentyl]-1*H*-imidazol-3-ium Hexafluorophosphate(V) (5-PF_6): A solution of KPF_6 (0.20 g,

1.09 mmol) in water (8 mL) was added to a stirred solution of **5-Br** (0.73 g, 0.95 mmol) in the same solvent (12 mL) at ambient temperature. The precipitate was filtered off, washed with water (2× 10 mL) and dried in vacuo (0.5 Torr) at 50 °C for 2 h to afford **5-PF$_6$** (0.62 g, 88%) as a colorless solid. M.p. 124 °C. $[\alpha]_D^{20}$ = +2.6 (*c* = 1, MeOH). ^{1}H NMR ([D$_6$]DMSO): δ = 9.10–9.04 (s, 1 H), 8.30 (m, 1 H), 7.94–7.58 (m, 3 H), 7.55–7.02 (m, 20 H), 5.31 (m, 1 H), 5.08 (m, 4 H), 4.99–4.94 (m, 1 H), 4.33–4.15 (m, 2 H), 4.13–3.83 (m, 2 H), 2.45–2.30 (m, 4 H), 2.07 (m, 2 H), 2.06–1.51 (m, 8 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 172.3, 170.9, 155.6, 140.7, 138.4, 136.9, 135.8, 127.9, 125.5–121.1 (Ar), 65.3, 59.0, 56.6, 48.5, 39.7, 39.5, 34.4, 33.1, 32.6, 31.8, 28.6, 24.4, 21.6, 20.9 ppm. HRMS: calcd. for $C_{42}H_{47}N_4O_5^+$ [M]$^+$ 687.3541; found 687.3548.

3-{5-[(1*S*,2*S*)-2-Amino-1,2-diphenylethylamino]-5-oxopentyl}-1-(4-carboxybutyl)-1*H*-imidazol-3-ium Hexafluorophosphate(V) (3): A mixture of 5% Pd/C (50 mg), **5-PF$_6$** (0.61 g, 0.82 mmol) and MeOH (10 mL) was stirred under H_2 (1 bar) at ambient temperature for 24 h. The catalyst was filtered off and washed with MeOH (10 mL). The combined filtrate and washings were concentrated under reduced pressure (10 Torr), and the residue was dried in vacuo (0.5 Torr) at 50 °C for 2 h to afford **3** (0.48 g, 96%) as a colorless solid. M.p. 103–105 °C. $[\alpha]_D^{20}$ = –24.58 (*c* = 1, MeOH). ^{1}H NMR ([D$_6$]DMSO): δ = 9.16 (s, 1 H), 8.45 (d, *J* = 8.1 Hz, 1 H, NH), 7.80 (d, *J* = 19.4 Hz, 2 H, CH), 7.31–7.07 (m, 10 H), 5.00 (t, *J* = 8.1 Hz, 1 H, CH), 4.29–3.81 (m, 5 H, CH$_2$, CH), 2.28–1.86 (m, 4 H, CH$_2$), 1.80–1.36 (m, 8 H, CH$_2$) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 174.6, 171.3, 141.7, 135.9, 128.9–126.5 (Ar), 122.4, 71.3, 59.3, 58.6, 48.6, 34.3, 33.3, 28.9, 26.6, 25.3, 22.3, 21.3 ppm. HRMS: calcd. for $C_{27}H_{35}N_4O_3^+$ [M]$^+$ 463.2700; found 463.2704.

General Procedure for the Michael Reaction: A mixture of 4-hydroxy-2*H*-chromen-2-one (**6**; 16.2 mg, 0.1 mmol), α,β-unsaturated ketone **7** (0.12 mmol), catalyst **3** (12.2 mg, 0.02 mmol), AcOH (30 μL) and THF (150 μL) was stirred at ambient temperature for the period specified in Tables 1 and 2. After the reaction was complete (TLC monitoring), the solvent and AcOH were removed under reduced pressure, and the residue was extracted with Et$_2$O (5× 10 mL). The combined extracts were concentrated under reduced pressure (10 Torr), and products **8** were purified by column chromatography (silica gel; eluent *n*-hexane/EtOAc = 3:1, then EtOAc). Analytical data for new compounds **8c**–**g** are given below.

(*S*)-4-Hydroxy-3-[3-oxo-1-(pyridin-3-yl)butyl]-2*H*-chromen-2-one (8c): Colorless solid (29.9 mg, 97%). M.p. 193–195 °C. 70% *ee*; the *ee* value of the product was determined by HPLC by using an AD-H column (*n*-hexane/*i*PrOH = 7:3), flow rate 0.7 mL/min^{-1}, λ = 254 nm, t_R = 6.35 (minor), 8.38 (major) min. $[\alpha]_D^{25}$ = +1.55 (*c* = 1.0, CH_2Cl_2). ^{1}H NMR ([D$_6$]DMSO): δ = 8.50 (m, 1 H), 8.39 (m, 1 H), 7.85 (m, 1 H), 7.64 (m, 2 H), 7.50–7.19 (m, 4 H), 4.06 (m, 1 H), 2.34 (m, 1 H), 1.96 (s, 1 H), 1.67–1.61 (s, 2 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 211.2, 152.4, 148.7–146.7 (2 C), 139.5, 135.0, 131.9, 123.9–122.9 (3 C), 116.2, 102.7–100.4 (2 C), 42.4, 32.9, 30.6, 27.3 ppm. HRMS (ESI): calcd. for $C_{18}H_{16}NO_4^+$ [M + H]$^+$ 310.1074; found 310.1088.

(*S*)-3-(1-Cyclohexyl-3-oxobutyl)-4-hydroxy-2*H*-chromen-2-one (8e): Colorless solid (23.5 mg, 75%). M.p. 63–64 °C. 90% *ee*; the *ee* value of the product was determined by HPLC by using an AD-H column (*n*-hexane/*i*PrOH = 7:3), flow rate 0.7 mL/min^{-1}, λ = 220 nm, t_R = 7.32 (major), 5.83 (minor) min. $[\alpha]_D^{25}$ = –61.07 (*c* = 1.0, MeOH). ^{1}H NMR ($CDCl_3$): δ = 7.93 (m, 1 H), 7.48 (m, 1 H), 7.26 (m, 2 H), 3.36–3.17 (m, 1 H), 3.09–2.74 (m, 2 H), 2.28–2.10 (m, 4 H), 1.95–1.83 (m, 1 H), 1.82–1.44 (m, 7 H), 1.37–1.07 (m, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 214.4, 161.7, 152.7, 131.5, 123.9, 116.7–116.1 (2 C), 107.3, 44.9, 36.9, 36.1, 32.9, 32.0, 31.8, 29.9, 26.3, 26.1, 26.00 ppm. HRMS (ESI): calcd. for $C_{19}H_{23}O_4^+$ [M + H]$^+$ 315.1591; found 315.1595 and for $C_{19}H_{22}O_4Na^+$ [M + Na]$^+$ 337.1410; found 337.1404.

(*S*)-3-[1-(Ferrocenyl)-3-oxo]-4-hydroxy-2*H*-chromen-2-one (8f): Yellow solid (29.1 mg, 70%). M.p. 104 °C (dec.). 51% *ee*; the *ee* value of the product was determined by HPLC by using an AD-H column (*n*-hexane/*i*PrOH = 99:1), flow rate 0.7 mL/min^{-1}, λ = 254 nm, t_R = 9.19 (minor), 13.08 (major) min. $[\alpha]_D^{25}$ = +23.20 (*c* = 1.0, MeOH). ^{1}H NMR ($CDCl_3$): δ = 9.27 (m, 0.3 H), 7.88 (m, 1 H), 7.48 (m, 2 H), 7.25 (m, 2 H), 4.49–3.92 (m, 11 H), 3.40 (m, 1 H), 2.41–1.94 (m, 4 H), 1.64 (m, 2 H), 1.26 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 212.8, 160.3, 131.7, 123.9, 116.5, 116.2, 107.9, 88.6, 69.8–67.3 (9 C), 46.9, 28.2–31.3 (3 C) ppm. HRMS (ESI): calcd. for $C_{23}H_{20}O_4Fe^+$ [M + H]$^+$ 416.0706; found 416.0702.

(*S*)-3-[1-(Cymantrenyl)-3-oxo]-4-hydroxy-2*H*-chromen-2-one (8g): Yellow solid (30.5 mg, 70%). M.p. 110 °C (dec.). 72% *ee*; the *ee* value of the product was determined by HPLC by using an AD-H column (*n*-hexane/*i*PrOH = 7:3), flow rate 0.7 mL/min^{-1}, λ = 220 nm, t_R = 5.99 (minor), 7.80 (major) min. $[\alpha]_D^{25}$ = +18.47 (*c* = 1.0, MeOH). ^{1}H NMR ($CDCl_3$): δ = 9.60 (m, 1 H), 7.96 (m, 1 H), 7.79 (m, 1 H), 7.52 (m, 2 H), 7.28 (m, 4 H), 5.30 (m, 1 H), 5.07 (m, 1 H), 4.80–4.46 (m, 5 H), 4.29–4.07 (m, 2 H), 3.89–3.53 (m, 2 H), 3.26–2.96 (m, 2 H), 2.52–2.12 (m, 5 H), 2.09–1.68 (m, 4 H), 1.43–1.13 (m, 3 H) ppm. ^{13}C NMR ([D$_6$]DMSO): δ = 215.8 (4 C), 162.9, 142.3, 134.2, 126.8, 96.7, 90.5, 90.0, 53.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{15}MnO_7Na^+$ [M + Na]$^+$ 457.0090; found 457.0039.

Catalyst Recovery: The catalyst that had remained after extraction of product **8** with Et$_2$O was dried under reduced pressure (1.0 Torr) for 30 min; fresh portions of **6** (16.2 mg, 0.10 mmol), **7a** (17.5 mg, 0.12 mmol), AcOH (30 μL) and THF (150 μL) were added, and the reaction was performed at ambient temperature for 24 h.

Supporting Information (see footnote on the first page of this article): Procedures for the preparation of each compound; ^{1}H, ^{13}C NMR and HR mass spectra as well as HPLC data.

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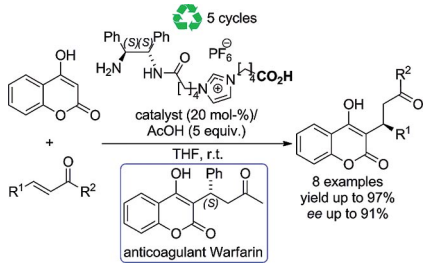
The sustainability of ionic-liquid-supported primary-amine-derived recyclable chiral organocatalyst of practical important in asymmetric Michael reactions has been improved by incorporating a peripheral carboxylic group that suppresses undesirable off-cycle reactions during the catalytic process.



Keywords: Synthetic methods / Asymmetric catalysis / Michael addition / Organocatalysis / Warfarin

