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A Highly Active Polymer-Supported Catalyst for Asymmetric Robinson Annulations in Continuous Flow

Santiago Cañellas,[†,‡] Carles Ayats,[†,‡] Andrea H. Henseler,[†] Miquel A. Pericàs*[,†,§]

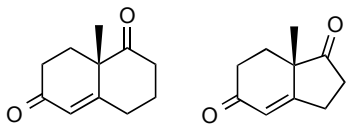
[†]Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology, Avda. Països Catalans 16, E-43007 Tarragona, Spain

[§]Departament de Química Inorgànica i Orgànica, Universitat de Barcelona, 08028 Barcelona, Spain

ABSTRACT: The preparation through Robinson annulation of enantiopure building blocks with both academic and industrial relevance, such as the Wieland-Miescher and Hajos-Parrish ketones, has suffered from important drawbacks, such as the need of high catalyst loading or extremely long reaction times. Here we report a heterogeneized organocatalyst based on Luo's diamine for the fast and broad-scope enantioselective Robinson annulation reaction. The polystyrene-supported diamine **19a** enables the high-yield, highly enantioselective preparation of a wide scope of chiral bicyclic enones under mild conditions, with reaction times as short as 60 minutes (batch) or residence times of 10 minutes (flow). In contrast with its homogeneous counterpart **19b**, the catalytic resin **19a** experiences a notable increase in catalytic activity with temperature in 2-MeTHF (a ten-fold decrease in reaction times without erosion in enantioselectivity is observed from room temperature to 55 ºC). The scope of the transformation in batch has been illustrated with 14 examples, including examples only reported in poorly enantioenriched (**22n**) or in racemic form (**22k**). Enantiopure **22k** has been used as starting material for a straightforward formal synthesis of the antibiotic and antifeedant sesquiterpene (–)-isovelleral (**24**). The heterogeneized catalyst **19a** admits extended recycling (10 cycles) and has been used to develop the first asymmetric Robinson annulations in continuous flow. The potential of the flow process is illustrated by the large scale preparation of the Wieland-Miescher ketone (65 mmol in 24 h operation, TON of 117) and by a sequential flow experiment leading to a library of eight enantioenriched diketone compounds.

KEYWORDS : Robinson annulation, Continuous flow, Heterogeneized catalysts, Wieland-Miescher ketone, Hajos-Parrish ketone

The Hajos-Parrish-Eder-Sauer-Wiechert (H-P-E-S-W) reaction to access chiral bicyclic enones, via an intramolecular aldol reaction, is one of the most well-known organocatalytic processes.[1] Reported in 1971 by two independent industrial research groups, this L-proline-catalyzed process enables the isolation of enantioenriched Wieland-Miescher (W-M, **1**) and Hajos-Parrish (H-P, **2**) ketones (Figure 1).[2] While high enantioselectivity was achieved for the H-P ketone (**2**), the W-M ketone (**1**) was obtained with moderate enantioselectivity. In both cases, prolonged reaction times were required.



W-M ketone, 1 **H-P ketone, 2**

Figure 1. Wieland-Miescher ketone (W-M ketone, **1**) and Hajos-Parrish ketone (H-P ketone, **2**).

Enantioenriched W-M and H-P ketones provide access to a broad variety of sesquiterpenoids, diterpenoids and steroids.[1b,3] Biological activities of these compounds include antimicrobial, anticancer, antiviral and antineurodegenerative effects.[3] For these reasons, since 2000, following the seminal work by List and Barbas on the use of proline as a catalyst for enantioselective aldol reaction,[4] there has been a resurgent interest in achieving more efficient routes for these catalytic processes.[5] As a result, several new organocatalysts have emerged for the synthesis of these bicyclic enones.[3a-b] Among them, most structures are based on chiral amines for promoting the reaction through enamine activation mode.

For instance, proline-catalyzed "one-pot" procedures,[6] cyclic-amino acid (1*R*,2*S*)-cispentacin,[7] amino acids and short α/β-peptides,[8] bimorpholine derivatives,[9] prolinamide,[10] prolinethiomide,[11] 1,2-cyclohexanediamine derivatives,[12] binaphthylprolinamides,[13] and chiral vicinal-diamines[14] have been developed. Recently, a BINOL-derived phosphoric acid[15] was also reported as organocatalyst to perform this transformation through hydrogen-bonding activation mode (For some examples, see Figure 2).

Most of the aforementioned organocatalysts were able to perform the synthesis of W-M and H-P ketones, however important drawbacks such as high catalyst loading, limited scope or very long reaction times (from 10 hours to 7 days) are present in all cases.[6-15] Importantly, the chiral

vicinal-diamine developed by Luo[14,16] promoted Robinson annulation reactions very efficiently, leading to a series of chiral bicyclic enones in very high yield and stereoselectivity in notably short reaction times (12-24 hours).

Practical applications of homogeneous asymmetric catalysis in industrial processes are limited due to issues associated with high cost of chiral catalysts. Catalyst immobilization onto solid supports can be a feasible approach as catalysts can be isolated from the reaction mixture by simple filtration, and the recovered catalyst can be reused repeatedly during consecutive catalytic cycles.[17] Additionally, heterogeneized catalysts can be applied in continuous flow processes with the advantage of not being co-eluted during the process.[18,19] Moreover, the alleged limitations of immobilized metal catalysts,[20] mostly centered on metal leaching, should not apply with covalently bonded organocatalysts.

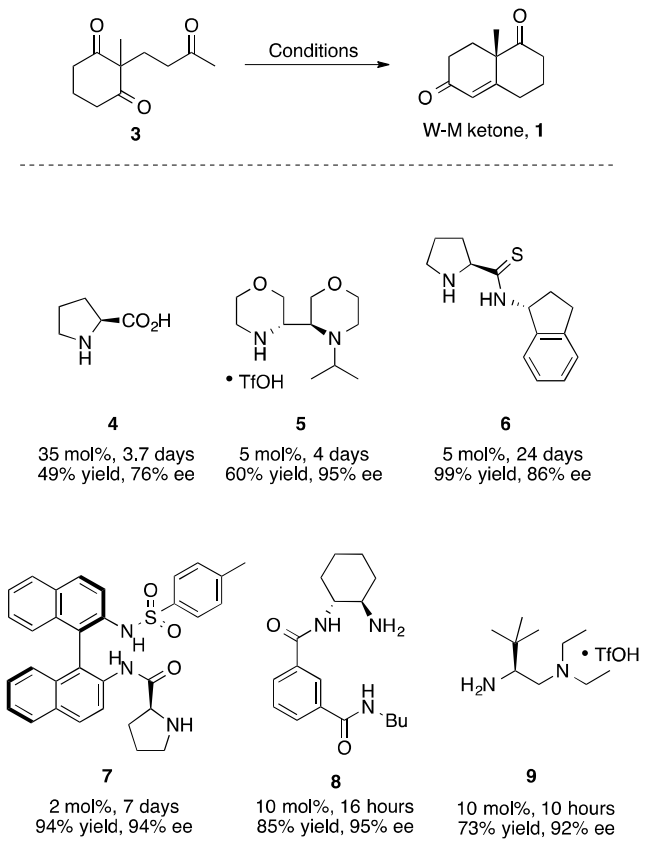


Figure 2. Selected organocatalysts for the synthesis of W-M ketone through enamine activation mode.[6b,9,11,13a,12a,14]

Considering the advantages of heterogenized catalysts, and the high volume of reports regarding new organocatalysts for enantioselective formation of W-M and H-P ketone derivatives,[3a-b,6-15] it is surprising that only few approaches have been reported dealing with the development of immobilized catalysts applicable to this transformation. In addition, all of them require extremely prolonged reaction times, and either moderate results or non-recyclability of the catalysts is recorded.[21]

In response to these unmet demands, that could greatly facilitate the preparation of important enantiopure building blocks (e.g., the W-M and H-P ketones),[3] herein we report the preparation of a highly-active polymer-supported chiral vicinal-diamine catalyst for the asymmetric preparation of bicyclic diketones through the Robinson protocol in batch and flow. This is, to the best of our knowledge, the first implementation of this important transformation in continuous flow. Through its application, the large-scale synthesis of the W-M ketone, as well as the sequential preparation of a library of W-M and H-P type diketones derivatives, are implemented in a highly productive, single-pass continuous flow process.

RESULTS AND DISCUSSION

Inspired by the success of Luo's report for using the triflate ammonium salt of chiral vicinal-diamine **9**,[14] we considered the opportunity of developing an immobilized version of this catalyst that could add to the properties of **9** the possibility of extended recycling and reuse.

Our design principle (Figure 3) involved modification of the diethylamino fragment in order to introduce a *handle* that could allow immobilization with minimal perturbation of the enantiodiscriminating transition state in the key aldol reaction. After extensive experimentation, we identified the polymer-supported derivative **19a** as a most promising catalyst candidate for the synthesis of W-M and H-P ketone derivatives.

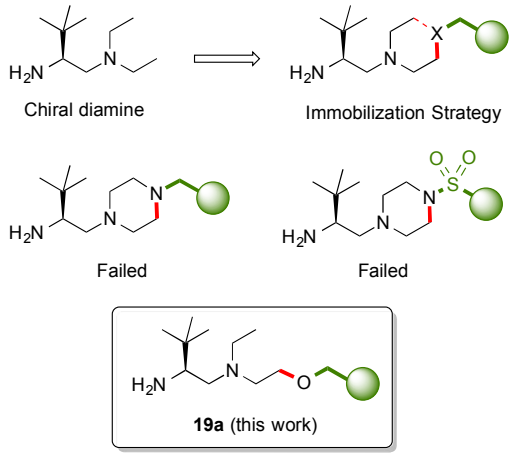
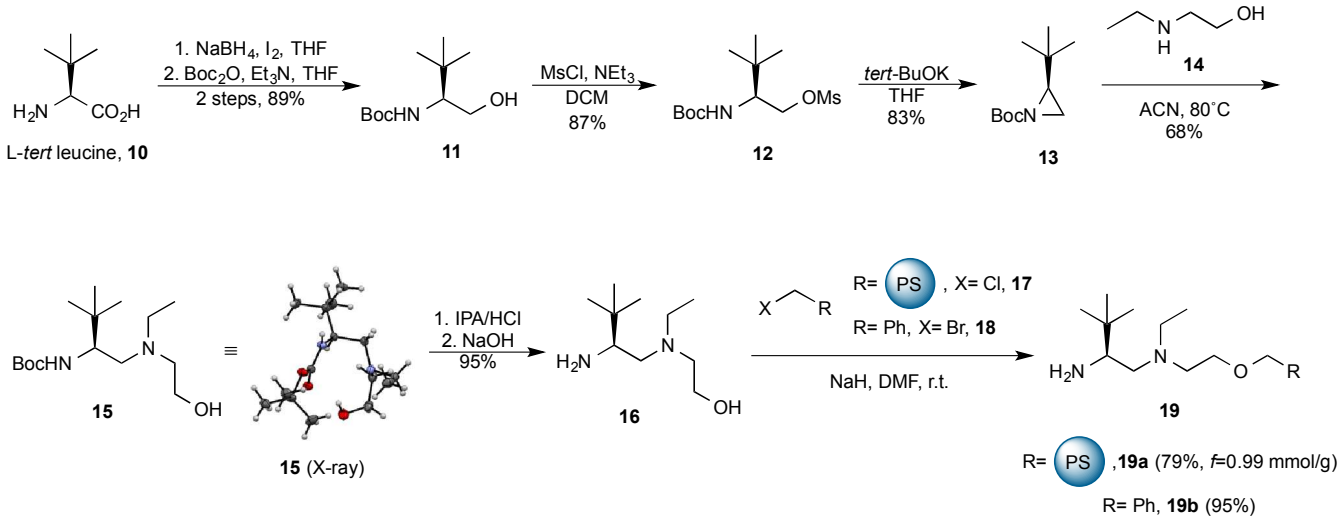


Figure 3. Design principle followed in this study and candidate evolution towards **19a**.

The preparation of **19a** from L-*tert*-leucine is shown in Scheme 1. For comparison purposes, the homogeneous analogue **19b** was also prepared. Starting from commercially available L-*tert*-leucine **10**, reduction with sodium borohydride in the presence of iodine,[22] produced an amino-alcohol which was *N*-protected with Boc_2O under basic conditions to afford (*S*)-*N*-Boc *tert*-leucinol **11** in 89% yield (2 steps).[23] Mesylation of the Boc-protected amine **11**[24] and subsequent cyclization with potassium *tert*-butoxide[25] afforded the desired aziridine **13** in 72% Yield (2 steps).[26] Ring-opening with the 2-(ethylamino)ethanol **14** led to the desired *N*-Boc amino alcohol **15** (68% yield), whose structure could be confirmed by X-ray crystallographic analysis.[27] Acid-mediated Boc deprotection of **15** gave rise to amino-alcohol **16** in good yield (95% yield). Ultimately, **16** could be tethered to

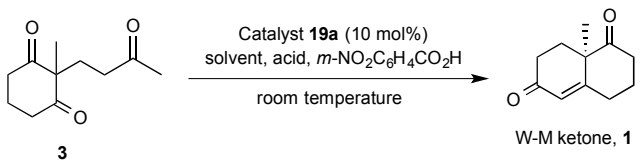
microporous polystyrene *via* nucleophilic substitution of the chlorine atoms of commercially available Merrifield resin **17** (1% DVB, f = 1.55 mmol/g) to afford **19a** with high immobilization yield (f = 0.99 mmol/g, f_{max} = 1.25 mmol/g, 79%). Likewise, the homogeneous catalyst **19b** could be prepared in very good yield (95%) from **16** and benzyl bromide **18**.

With heterogeneized catalyst **19a** in hand, its use was initially optimized under batch conditions for the formation of W-M ketone **1**, from the corresponding triketone **3** (Table 1).



Scheme 1. Synthesis of the PS-Supported catalyst **19a** and the homogeneous analogue **19b**.

Table 1. Optimization of the reaction conditions for **19a**.[a]



Entry	Solvent	Acid (x mol%)	*m*-NBA (x mol%)	**1** (%)[b]	ee (%)[c]
1	DCM	TfOH (10)	-	35	94
2	DMF	TfOH (10)	-	61	94
3	DMF:H_2O	TfOH (10)	-	54	95
4	THF	TfOH (10)	-	66	95
5	THF	TFA (10)	-	61	94
6	THF	AcOH(10)	-	32	77
7	THF	CSA (10)	-	22	89
8	THF	-	10	90	91
9	THF	TfOH (15)	-	58	92
10	THF	TfOH (10)	5	99	92
11[d]	2-MeTHF	TfOH (10)	5	94	93
12[d,e]	2-MeTHF	TfOH (10)	5	99	91

[a]Reactions performed at room temperature in a High-Throughput Experimentation (HTE) facility using triketone **3** (50 µmol), catalyst **19a** (10 mol%) and solvent (1M). Reaction time: 12 hours. [b]HPLC yields determined by using naphthalene as internal standard. [c]Determined by HPLC on the crude reaction mixture using a chiral stationary phase. [d]Bench reaction conditions: triketone **3** (0.14 mmol), catalyst **19a** (10 mol%) and 2-MeTHF (1M). [e]Temperature: 55 ºC and 1 hour reaction.

Screening of different parameters, such as solvents, acids for the preformation of the ammonium salt of **19a** and additives was performed in a High-Throughput Experimentation (HTE) platform (see Table S1 for a more detailed account). The catalytic activity of resin **19a** was comparable in all tested solvents, high values of enantiomeric excesses (>90% ee) being recorded in all cases (Table 1, entries 1-4). Regarding reactivity, however, reactions performed in DCM were considerably slower than in DMF, DMF:H_2O and THF. The catalytic activity also showed a dependence on the pK_a of the acids used to form the ammonium salt of **19a**, which is active catalyst. After some experiments with different acids, we selected the strongest acid tested (triflic acid, 10 mol%) as the best option (Table 1, entries 4-8). Furthermore, with the addition of a mild acid such as *m*-$NO_2C_6H_4CO_2H$ (5 mol%) as an additive, better results were recorded in comparison with experiments where an excess of strong acid was used (Table 1, entries 9-10). This enhancement of reactivity can be rationalized by considering acid-facilitated iminium-enamine tautomerization.[14b] This observation is consistent with previous reports by Luo.[14]

Observing the good catalytic activity in THF, a greener solvent, 2-MeTHF was also tested. Gratifyingly, similar results were also recorded, therefore future experiments were performed in 2-MeTHF (Table 1, entry 11).

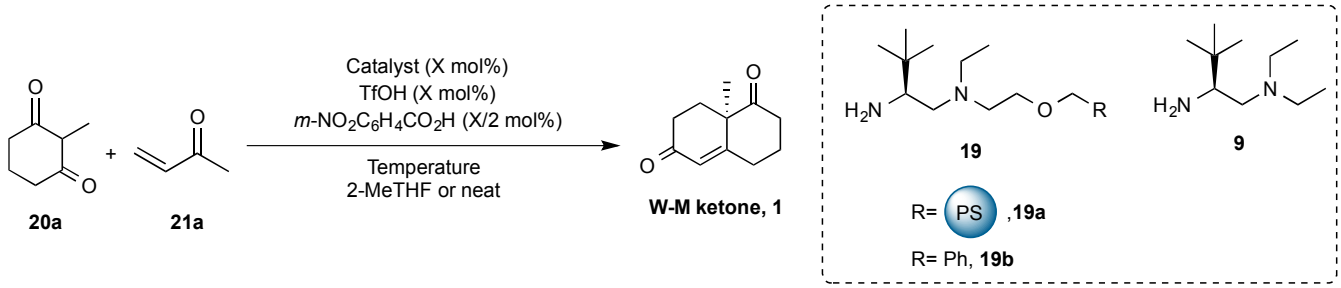
Although high yield and enantiomeric excesses could be achieved under this set of reaction conditions, we sought the possibility of decreasing reaction time by modifying the reaction temperature. To our delight, the reaction was impressively fast at 55 ºC, triketone **3** being consumed in just 1 hour with practically no erosion in enantioselectivity (Table 1, entry 12).

We next examined the possibility of achieving the Wieland-Miescher ketone **1** through Robinson annulation reaction between commercially available diketone **20a** and methyl vinyl ketone **21a**. By employing the same optimized conditions for triketone **3** as starting material (10 mol% of **19a**, 10 mol% TfOH, 5 mol% *m*-$NO_2C_6H_4CO_2H$, 55 ºC), full conversion of diketone **20a** was also achieved in just 1 hour without decrease in enatioselectivity (Table S4). To the best of our knowledge, the present procedure shortens by one order of magnitude the reaction times of the best previous procedures (more than 10 hours required)[14] for the preparation of the Wieland-Miescher ketone **1** while keeping excellent levels of enantiocontrol (more than 90% ee).

As aforementioned, reaction temperature was a crucial parameter in this highly optimized Robinson annulation procedure mediated by **19a**. To understand this temperature effect, some comparative experiments were performed under the same conditions with the homogeneous catalysts **19b** and **9**. Since solvent is needed when using PS-Supported catalysts, these reactions were also performed in 2-MeTHF. It is important to note that reactions in 2-MeTHF mediated by **19b** and **9** were remarkably slower than those performed under the standard neat conditions (Table 2, entries 2-5, 6-11). A solvent dependence observed with catalyst **9** was already reported in the literature.[14a] All three catalysts, **19a**, **19b** and **9** had same behavior when reactions were performed at room temperature (Table 2, entries 2, 8 and 13); however, important deviations in activity were detected when temperature changed. Surprisingly, the previously observed enhancement in the reactivity at higher temperatures for **19a** was not as pronounced for the homogeneous variants **19b** and **9**. For instance, when the reaction is performed at 60 ºC for 12 hours, very good yield and enantioselectivity was obtained using PS-Supported catalyst **19a** (Table 2, entry 12). In contrast, homogeneous catalysts **9** and **19b** achieved inferior results in 72 hours at the same temperature under neat conditions (Table 2, entries 1 and 6). For reactions in 2-MeTHF, the reactivity of the homogeneous catalysts was even lower (Table 2, entries 5 and 7). The enhanced reactivity of the resin **19a** when increasing temperature likely reflects a beneficial effect of the non-polar polystyrene environment on the activity of the supported catalysts. While this effect could be somewhat masked by mass transfer limitations at room temperature, it becomes fully operational at 55-60 ºC. Similar beneficial effects have been previously noted and could be reminiscent of those found in the active sites of enzymes.[28] The polymeric matrices have been shown to very efficiently increase the local concentration of both substrates within the confined reaction pocket present on them[29] and, in this case, higher temperatures could activate the molecules inside the hydrophobic pockets much more efficiently than in solution.

Encouraged by these results, we next turned our attention to explore the catalytic scope of **19a** in Robinson annulation reactions leading, among other, to W-M and H-P ketone derivatives (Scheme 2).

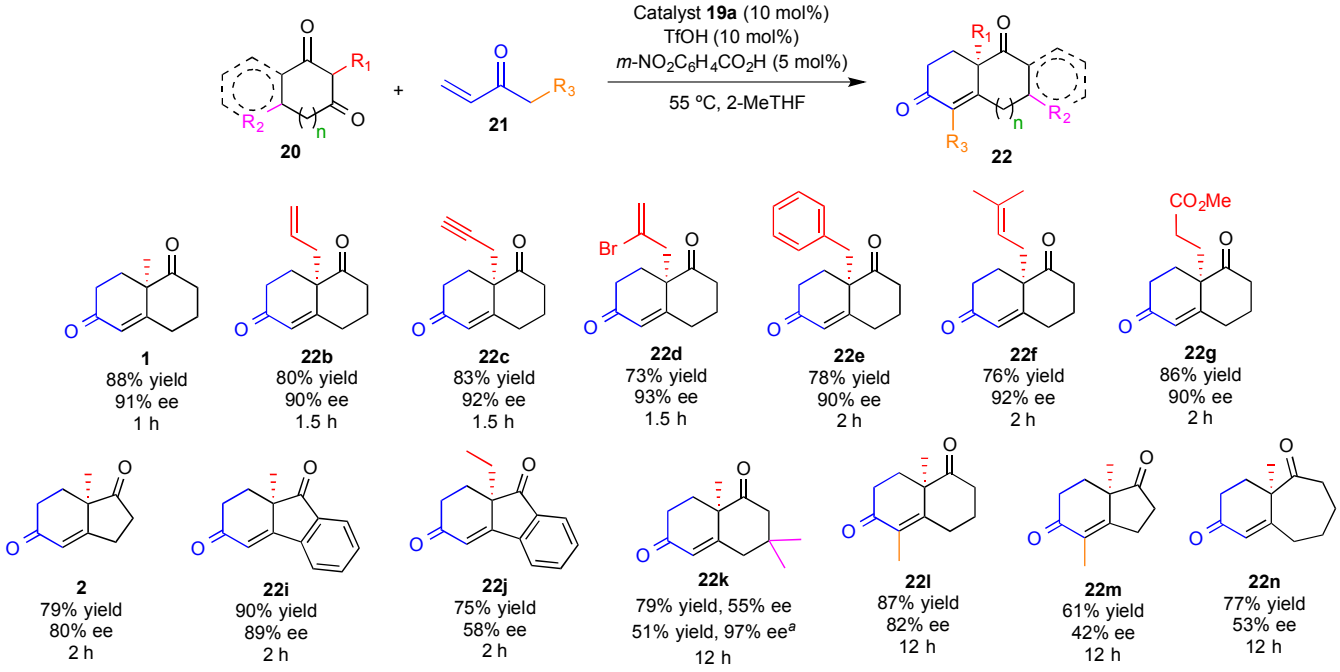
Table 2. Screening conditions comparing homo- and heterogeneous catalysts for Robinson annulation reaction.[a]



Entry	Catalyst (mol %)	Time (h)	Temperature (ºC)	Solvent	Yield (%)[b]	ee (%)[c]
1[d]	**9** (2 mol%)	72	60	neat	87	90
2[e]	**9** (10 mol%)	10	r.t.	neat	73	92
3	**9** (10 mol%)	24	r.t.	2-MeTHF	traces	nd
4	**9** (10 mol%)	6	55	neat	50	90
5	**9** (10 mol%)	6	55	2-MeTHF	28	89
6	**19b** (2 mol%)	72	60	neat	72	89
7	**19b** (2 mol%)	96	60	2-MeTHF	45	89
8	**19b** (10 mol%)	16	r.t.	neat	80	94
9	**19b** (10 mol%)	48	r.t.	2-MeTHF	42	92
10	**19b** (10 mol%)	1	55	neat	65	90

11	**19b** (10 mol%)	2	55	2-MeTHF	62	90
12[f]	**19a** (2 mol%)	12	60	2-MeTHF	93	90
13	**19a** (10 mol%)	10	r.t.	2-MeTHF	88	93
14	**19a** (10 mol%)	1	55	2-MeTHF	88	91

[a]Reaction conditions: 2-methyl-1,3-cyclohexanedione **20a** (0.27 mmol), methyl vinyl ketone **21a** (0.32 mmol), catalyst (2 or 10 mol%), TfOH (2 or 10 mol%), *m*-$NO_2C_6H_4CO_2H$ (1 or 5 mol%), 2-MeTHF (0.27 mL) or neat. [b]Isolated yields. [c]Determined by performing HPLC using a chiral stationary phase of the crude mixture. [d]2-Methyl-1,3-cyclohexanedione **20a** (7.9 mmol) and methyl vinyl ketone **21a** (9.48 mmol) were used. [e]2-Methyl-1,3-cyclohexanedione **20a** (0.5 mmol) and methyl vinyl ketone **21a** (0.6 mmol) were used. [f]2-Methyl-1,3-cyclohexanedione **20a** (3.96 mmol) and methyl vinyl ketone **21a** (4.76 mmol) were used.



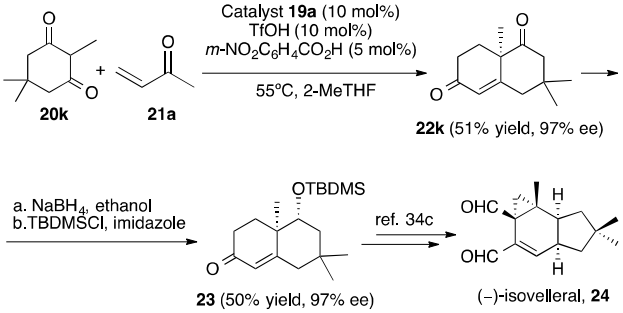
Scheme 2. Robinson annulation reaction scope. Isolated yields. [a]After recrystallization.

Bicyclic diketones of the [4.4.0] type (W-M type) bearing a variety of substituents at carbon 8a in the ring junction (**1**, **22b-g**), were prepared in short reaction times (1-2 hours) and very high enantiomeric excesses (up to 93%). The method also allowed to achieve H-P ketone **2** in only 2 hours reaction time with yield and enantioselectivity similar to those reported in the literature. However, it is important to note that all previously reported procedures required prolonged reaction times (1-7 days).[6-14] Moreover, two H-P ketone derivatives bearing a condensed benzo ring (**22i** and **22j**) were also successfully prepared with very good results. The fluorene-based skeleton present in these compounds is of interest since it is present in many bioactive compounds such as agents for the treatment of brain edema[3oa] or selective Estrogen Receptor β-subtype (ERβ) agonists.[3ob]

Interestingly, substrate **22i** bearing a methyl group at position 8a has been obtained with a higher level of enantiocontrol compared to those reported by the analogous homogeneous catalyst **9** (65% ee).[14a] Furthermore, compound **22j** has been prepared for the first time using an enamine activation mode.[15] We also investigated the formation of C5-substituted bicyclic diketones **22l** and **22m**, previously prepared through amino acid promoted Robinson annulation.[8b] Interestingly, reactions catalyzed by **19a** were considerably faster, leading to **22l** in high yield and enantioselectivity. Not unexpectedly, results were more modest for **22m**. Resin **19a** also catalyzed the formation of the enantioenriched [5.4.0] bicyclic diketone **22n**. This unusual bicyclic core has been found in several natural products with attractive biological activities such as guanacastepenes and heptemer-

ones.[31] It should be noted that previous attempts at accessing enantioenriched **22n** using organocatalysis were unsuccessful.[32] The synthesis of this compound has been reported very recently using lipases as a biocatalyst, however very poor values of enantiomeric excess (8% ee) were achieved and extremely prolonged reaction times (8 days) were needed.[33] In our case, the 7-membered ring bicyclic enone **22n** was obtained in good yield (77%) and moderate enantiomeric excess (53%) in a rather short reaction time (12 h).

Interestingly, the enantioselective synthesis of **22k**, bearing a *gem*-dimethyl group at position-3 of the W-M ketone skeleton, has remained elusive in the literature. Several articles reported that attempts to obtain **22k** in optically active form following previously reported procedures developed for the asymmetric synthesis of the Wieland-Miescher ketone using chiral organocatalysts were unsuccessful.[34] In our hands, resin **19a** catalyzed the formation of compound **22k** in good yield and excellent enantioselectivity after crystallization. Importantly, ketone **22k** has been shown to be an interesting intermediate for the total synthesis of several natural products as furanether B and (+)-isovelleral **24**.[34a-c] Since previously reported organocatalysts failed to form enantioenriched **22k**, all reported routes towards synthesis of furanether B and (+)-isovelleral involved racemic synthesis of **22k** and subsequent enzymatic resolution of one advanced intermediate of **22k** by *Candida Rugosa* lipase (CRL). For instance, eight synthetic steps were needed to get protected alcohol **23**, a key intermediate for the synthesis of the natural antibiotic and antifeedant sesquiterpene from *Basidiomycetes* (+)-isovelleral **24**, in only moderate enantiomeric purity (83% ee).[34c] The use of **19a** for the direct preparation of enantioenriched frameworks like **22k** may provide many opportunities for the synthesis of attractive natural products which have remained elusive due to the low reactivity of the *gem*-dimethyl diketone **20k** in Robinson annulation. To illustrate this potential, we have successfully carried out a short formal synthesis of the equally active and less mutagenic enantiomer (–)-isovelleral **24**,[34d] using asymmetric Robinson annulation promoted by PS-Supported catalyst **19a** as the key step (Scheme 3).



Scheme 3. Formal synthesis of (–)-isovelleral using the PS-Supported catalyst **19a**.

Chemo- and diastereoselective reduction of the non-conjugated ketone moiety in **22k** with sodium borohydride and subsequent alcohol protection with *tert*-butyldimethylsilyl chloride gave rise to **23** in 50% overall yield and very high enantiomeric purity (97% ee).[35] In this manner, only three steps are required to obtain diastereo- and enantiomerically pure intermediate **23** from commercially available starting materials in contrast to the much longer (8 step) and less enantioselective synthesis reported in the literature.[34c]

One of the most important advantages offered by supported catalysts is the possibility to recover them by simple filtration and reuse them in a new catalytic cycle.[17] In order to test the robustness of the PS-Supported catalyst **19a**, recycling experiments in the model Robinson annulation reaction for the synthesis of W-M ketone **1** was performed. Initially, experiments were done using 2-methyl-1,3-cyclohexadione **20a** and methyl vinyl ketone **21a** (Scheme 2), however a significant decrease in the reactivity along cycles was observed and resin **19a** could only be recycled for 3 times with moderate results.[36] To understand the reason for catalyst deactivation, control experiments with the homogeneous catalyst **19b** were performed. In one of these tests, homogeneous catalyst **19b** was kept in contact with methyl vinyl ketone under the optimized reaction conditions. Careful analysis of the reaction mixture revealed the formation of mono and dialkylated derivatives of **19b** resulting from the aza-Michael addition to methyl vinyl ketone **21a**.[27] We considered this process as the most probable origin of the deactivation of **19a**. If this was the case, the deactivation could be avoided by simply performing the reactions from the *meso* triketone **3**. Indeed, much better recyclability of resin **19a** was observed, although a slight decrease in the reactivity was detected as the recycling progressed. By slightly adapting reaction conditions, very high yields and enantiomeric excesses were achieved in 10 consecutive reaction cycles by just increasing 15 minutes the reaction time from one to the next cycle (Table 3).

The great catalytic activity showed by the PS-Supported catalyst **19a** convert it into a suitable candidate for a continuous flow processing. The achievement of this goal, that has not even been considered before due to the long reaction times and high catalyst loadings normally associated to Robinson annulation, would exert an enormous impact on the potential use of this important methodology for production purposes. We accordingly set up our efforts to convert the enantioselective Robinson annulation mediated by **19a** into a continuous flow process.

Table 3. Recyclability experiments of the PS-Supported catalyst **19a**.[a]

Cycle	Time (h)	Conv. (%)[b]	Yield (%)[c]	ee (%)[d]
1	1	95	89	90
2	1.25	95	90	90
3	1.5	95	89	91
4	1.75	96	91	90
5	2	95	89	92

6	2.25	95	89	90
7	2.5	94	88	91
8	2.75	93	86	90
9	3	92	83	90
10	3.25	91	80	92

[a]Reactions performed using triketone **3** (0.27 mmol), catalyst **19a** (10 mol%), TfOH (10 mol%), *m*-$NO_2C_6H_4CO_2H$ (5 mol%) and 2-MeTHF as solvent (1M). [b]Determined by ^{1}H-NMR spectroscopy. [c]Isolated yield. [d]After purification.

Due to solubility issues, the solvent used during the continuous flow experiments was DMF.[37] Since the starting materials of the process (**20a** and **21a**) do not react in solution in presence of *m*-$NO_2C_6H_4CO_2H$, and one single catalyst is used for the whole transformation (Michael plus desimetrizing aldol reaction), we first tried to circulate a solution of diketone **20a**, methyl vinyl ketone **21a** and co-catalyst *m*-$NO_2C_6H_4CO_2H$ in DMF through a cartridge containing the pre-swollen catalyst **19a**. Not unexpectedly, the PS-Supported catalyst **19a** was also deactivated in continuous flow due to the aza-Michael side reaction discussed above. To avoid this problem, we decided to take advantage from PS-supported base catalysts to allow a simple, batch preparation of **3** in solution through a process involving minimal manipulation of the reaction crude. In this manner the deletereous methyl vinyl ketone would be completely consumed before the reactants would enter the reactor containing the catalytic resin **19a**. Some commercially available PS-Supported bases, such as PS-DIPEA, PS-piperazinomethyl and PS-DBU (Table S7), were tested with this purpose. PS-Supported DBU **25** turned out to be the catalyst of choice for this transformation, leading at 2 mol% loading to full conversion of an equimolar mixture of commercially available diketone **20a** and methyl vinyl ketone **21a** in only 4 h at 60 ºC. Very clean DMF solutions of Michael adduct **3** were obtained in this manner. A simple filtration for removal of particles in suspension was required for its use in the continuous flow process. Then, crude mixture was directly injected together with *m*-$NO_2C_6H_4CO_2H$ into the catalytic reactor.

The simple continuous flow set-up used for the continuous flow experiments is shown in Figure 4. A preformed DMF solution of **3** (see above) was combined with *m*-$NO_2C_6H_4CO_2H$ (5 mol%) and pumped through a size-adjustable MPLC jacketed glass column packed with 0.8 g (0.56 mmol, f = 0.7 mmol·g^{-1}) of **19a**. A back-pressure regulator at 1.3 bar was connected at the reactor outlet, and the catalytic reactor was heated to 60ºC for operation. The continuous flow process was monitored by recording ^{1}H-NMR spectra of aliquots of the eluting solution every hour. Although conversion showed a slight decrease along a 24 h experiment, we were able to keep conversion high through according modification of flow rate (Table S8). To our delight, this unprecedented enantioselective continuous flow process allowed the preparation of 11.7 g (65.5 mmol) of enantioenriched W-M ketone **1** in 24 hours of operation, corresponding to an impressive TON of 117.

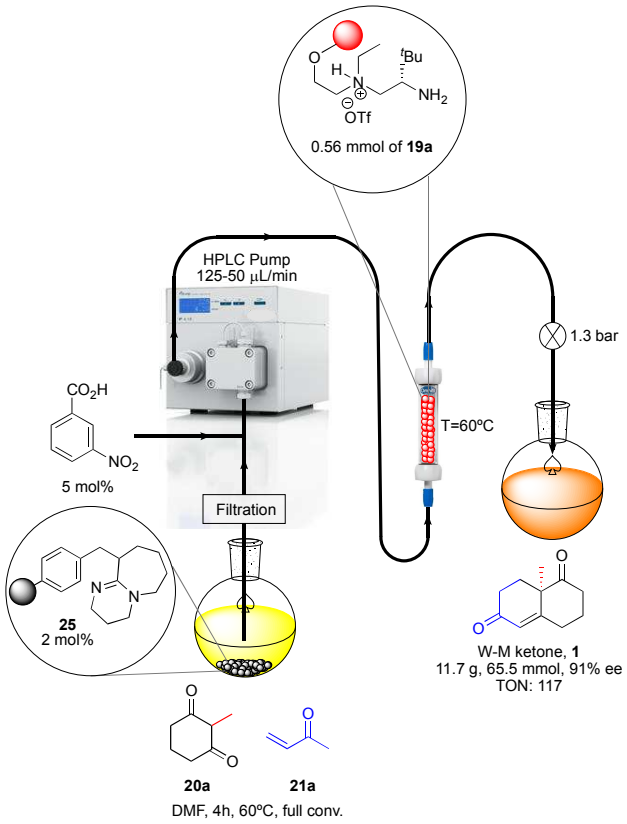


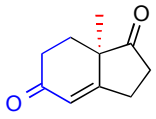
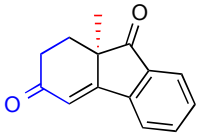
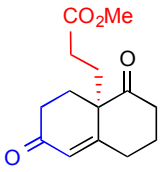
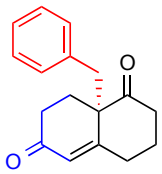
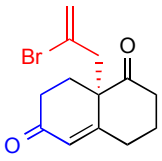
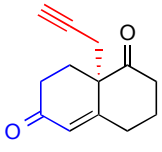
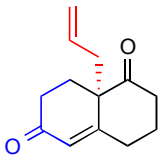
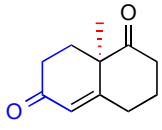
Figure 4. Set-up for the continuous flow Robinson annulation catalyzed for **19a**.

Catalytic asymmetric flow processes based on immobilized catalysts are of particular interest in diversity oriented synthesis, since a single set-up operation can be easily performed to prepare a library of enantiopure compounds in a sequential manner.[38] Taking advantage of the versatility of the PS-Supported vicinal diamine **19a**, a diverse library of enantioenriched Robinson annulation products was sequentially prepared using the set-up described above (Figure 4). As for the preparation of the W-M ketone, the starting materials were reacted in the presence of PS-DBU **25**, and the crude DMF solutions of *meso* triketones were filtered and directly injected into the catalytic reactor in combination with *m*-$NO_2C_6H_4CO_2H$. Each individual solution was circulated through the system for 30 minutes at 100 µL·min^{-1} (residence time: 10 minutes). For the avoidance of cross-contamination, the column was washed with DMF for 1 hour between the preparation of two consecutive products. Hence, eight enantioenriched bicyclic enones (H-P ketone **2**, **22i**, **22g**, **22e**, **22d**, **22c**, **22b** and W-M ketone **1**) were sequentially prepared (Table 4).

The diversity oriented continuous flow process was successfully carried out with very high productivities (TOF = 6.7-9.3 $mmol_{prod}$·$mmol_{resin}^{-1}$·h^{-1}) and afforded a library of Robinson annulation products with the same level of enantioselectivity recorded in batch (Scheme 2). From a practical perspective, the robustness of the resin is further verified by the fact that, after 7 consecutive

runs with different substrates, the W-M ketone **1** was prepared again (entry 8) with similar results to those recorded in the 24 h experiment in flow. Thus, resin **19a** could still be used with many more substrates as one would expect from a pre-packed catalyst cartridge.

Table 4. Diversity oriented asymmetric Robinson annulation in continuous flow.

Entry	Product	Yield (%)	TOF[a]	ee (%)[c]
1[b]	 **2**	84	9.0	78
2[b]	 **22i**	81	8.7	89
3[b]	 **22g**	87	9.3	90
4	 **22e**	84	9.0	92
5	 **22d**	79	8.4	93
6	 **22c**	62	6.7	94
7	 **22b**	63	6.8	92
8	 **1**	80	8.6	91

[a]TOF in $mmol_{prod} \cdot mmol_{resin}^{-1} \cdot h^{-1}$. [b]Treated with PS-$SO_3H$ to complete the dehydration step (2 mol%, 4h, 100ºC). [c]Determined by HPLC analysis of the reaction crude using a chiral stationary phase.

CONCLUSION

In summary, we have developed a PS-supported chiral vicinal diamine conceptually derived from Luo's catalyst that combines the selectivity performance of the homogeneous model with unique characteristics derived from its polymeric nature. Very high catalytic activity at convenient reaction temperatures and the possibility of extended recycling convert **19a** in the catalyst of choice for asymmetric Robinson annulations. Besides allowing the preparation of widely used building blocks, such as the enantioenriched W-M or the H-P ketones in very short reaction times (1-2 hours), **19a** also allows the convenient preparation of interesting and previously elusive enantioenriched bicyclic enones. In particular, adduct **22k** allows the straightforward preparation of an advanced intermediate in the synthesis of (–)-isovelleral with important step economy over previous approaches. The remarkable catalytic activity/enantioselectivity/recyclability profile of **19a** has eventually led to the development of the first Robinson annulation in continuous flow. Its application in the multigram synthesis of the enantioenriched W-M ketone or in the sequential preparation of a diverse library of Robinson annulated products show the potential of simple, pre-packed columns of resin **19a** as re-usable, multipurpose reactors for this academically and industrially relevant transformation in flow.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data (PDF)
Crystallographic data (CIF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: mapericas@iciq.es.

Author Contributions

‡ S. C. and C. A. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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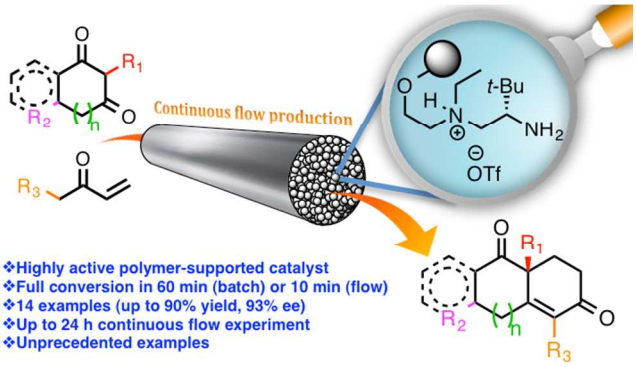
(35) The reaction conditions for these two steps have not been optimized.

(36) 1st cycle: 98% yield. 2nd cycle: 89% yield, 3rd cycle: 65% yield.

(37) Similar results were observed when using DMF instead of 2-MeTHF. See SI for more details (Table S1).

(38) For example, see: (a) Pericàs, M. A.; Herrerías, C. I.; Solà, L. *Adv. Synth. Catal.* **2008**, 350, 927–932. (b) Kasaplar, P.; Rodríguez-Escrich, C.; Pericàs, M. A. *Org. Lett.* **2013**, *15*, 3498–3501. (c) Ayats, C.; Henseler, A. H.; Dibello, E.; Pericàs, M. A. *ACS Catal.* **2014**, *4*, 3027–3033. (d) Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericàs, M. A. *Chem. Eur. J.* **2014**, *20*, 2367–2372.

TOC Graphic


Continuous flow production
t-Bu
NH2
OTf
❖Highly active polymer-supported catalyst
❖Full conversion in 60 min (batch) or 10 min (flow)
❖14 examples (up to 90% yield, 93% ee)
❖Up to 24 h continuous flow experiment
❖Unprecedented examples