DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

Silicone-supported Cinchona alkaloid derivatives as insoluble organocatalysts in the enantioselective dimerization of ketenes.

Damiano Cancogni,[a] Alessandro Mandoli,*[a] Ravindra P. Jumde,[a] and Dario Pini.[a]

Keywords: Asymmetric Catalysis / Cinchona Alkaloids / Ketene Dimerization / Organocatalysis / Silicones / Supported Catalysts

A straightforward procedure is presented for the covalent immobilization of ester and silyl ether derivatives of the *Cinchona* alkaloid 10,11-dihydroquinidine within insoluble cross-linked silicone elastomeric films. The materials prepared by this approach were effective heterogeneous organocatalysts in the asymmetric dimerization of ketenes, providing chiral Weinreb β- ketoamides in 28-83% yield and 79-99% ee in the course of several recycles. A productivity/enantioselectivity protocol is also proposed for a better assessment of the relative merits of soluble and supported asymmetric catalytic systems towards process intensification.

[a] Dipartimento di Chimica e Chimica Industriale, Università di Pisa, and CNR – ICCOM (Section of Pisa), Via Risorgimento 35, 56126, Pisa, Italy
Tel.: (+39)-050-221-9231
Fax: (+39)-050-221-9260
E-mail: alexm@dcci.unipi.it
Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

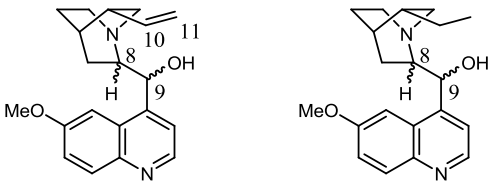
Introduction

Starting in the early 70's, the increasing use of homogeneous enantioselective catalysis has been accompanied by the development of covalently immobilized analogues.[1] Stemming from the exploration of alternative anchoring strategies, chiral derivatives and support materials, a large number of effective *insoluble polymer-bound* (IPB) catalysts or ligands are thus known at present to convincingly demonstrate the viability of the approach at the proof-of-concept level and clarify some important design elements required for the attainment of high catalytic activity and enantioselectivity.

Nonetheless, the hesitation to adopt this strategy for practical-scale applications seems still strong.[1b] Arguably this reluctance is partially dictated by cultural motivations, but it is also reasonable to say that the lack of evidence for decisive practical advantages in the use of the supported catalysts concurs to sustain it.[1h,2] In this regard, a common concern for most of the disclosed IPB systems is about their preparation, which often appears too complex or poorly efficient for any realistic scale-up planning. Even when this is not the case, the limited efforts put in studying catalyst recycling can be another problem that hampers a clear-cut answer to the question whether the repeated use of IPB systems can actually pay back for their generally more onerous obtainment.

To further complicate this judgment, within some limits the repeated use of an IPB catalyst may have an overall outcome analogous to the reduction of the loading of a homogeneous one, i.e. the increase of the productivity *P* (defined as the moles of product obtained per mole of catalyst) and the decrease of the *ee* values.[3] Provided some reduction of the stereochemical purity of the product can be tolerated at the synthesis stage, the use of diminished amounts of the soluble system may then be considered an equally valid option for process intensification, as opposite to the development of supported analogues. Under these circumstances, it is clear that for the field to improve its credibility proper comparison protocols have to be implemented and thoroughly used in this kind of studies.

The general considerations stated above hold true when the specific area of ligands and organocatalysts derived from the *Cinchona* alkaloids **1**-**4** (Figure 1)[4] is considered. In fact, by ingeniously exploiting the polyfunctional nature of the alkaloid core and alternative immobilization techniques, a large array of IPB alkaloid architectures have been reported,[1a-h,3,5] some of which are summarized in the Figure 2. However, with a few exceptions where the native alkaloids (or simple derivatives thereof) were effectively coupled to commercially available functional resins (*e.g.* **5** and **6**),[5d-f] the preparation of most of the disclosed materials appears largely unpractical. Typically, this was a consequence of the lengthy reaction schemes and repeated purifications in the synthesis of anchorable alkaloid derivatives (*e.g.* **10**)[3] or the low immobilization yield and the limited alkaloid loading attained in the actual immobilization step (*e.g.* **8** and **9**).[5a,5c] As pointed out also by Kacprzak and Lindner in a work on *Cinchona* alkaloid-based chiral stationary phases,[6] the development of IPB alkaloid derivatives for practical uses would therefore require a stronger emphasis on the efficiency of their preparation.



1 (8R,9S): QD-H
2 (8S,9R): QN-H
3 (8R,9S): DHQD-H
4 (8S,9R): DHQN-H

Figure 1. Structure, acronyms, and numbering scheme of the *Cinchona* alkaloids discussed in this work.

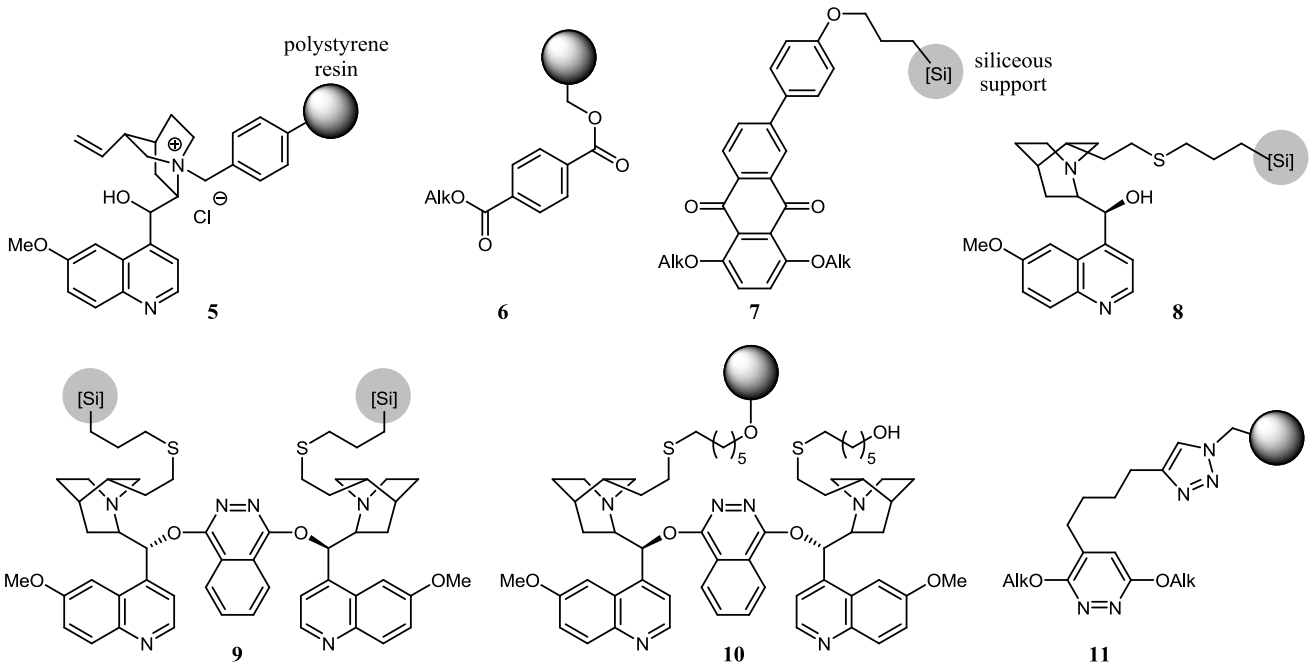


Figure 2. Typical anchoring positions for *Cinchona* alkaloid derivatives and selected IPB material architectures (AlkO = QD, QN, DHQD, or DHQN – see Figure 1).

With this aim we recently developed a new protocol for the access to the dimeric alkaloid derivatives linked to gel-type or macroporous polystyrene supports.[5g] That strategy proved highly effective in many respects, including a scalable preparation of the anchorable derivatives and their efficient coupling to preformed resins in a *click-chemistry* step. Moreover, the resulting materials **11** turned out to be remarkable organocatalysts in the asymmetric dimerization of ketenes described by Calter and co-workers,[7] affording chiral Weinreb β-ketoamides in 90-97% *ee* in the course of 20 reaction cycles.[5g]

Nonetheless, the relatively complex structure of **11** appears not strictly required for the aforementioned reaction because simpler monomeric 9-*O* alkaloid derivatives, like the propionate esters (Prop) and the trimethylsilyl (TMS) or *tert*-butyldimethylsilyl (TBDMS) ethers are equally effective organocatalysts.[7a,b,7f] In addition, whilst polystyrene resins provide the IPB systems in the form of reasonably robust *beads*, in the case of immobilized bis-oxazoline (Box) ligands we[8] and the group of Nagashima[9] recently found that the switch to cross-linked silicone supports could present some advantages in terms of handling and catalytic performances.

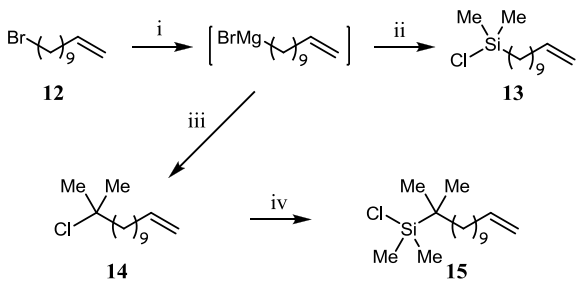
These considerations prompted us to investigate the covalent immobilization of monomeric 9-*O* derivatives of 10,11-dihydroquinidine (DHQD-H, **3**) within insoluble elastomeric silicone films and their use as organocatalysts in the heterogeneous asymmetric dimerization of ketenes. In the course of this study, the problem of comparing the IPB systems with their soluble counterpart was also addressed, leading to the results presented in the following sections.

Results and Discussion

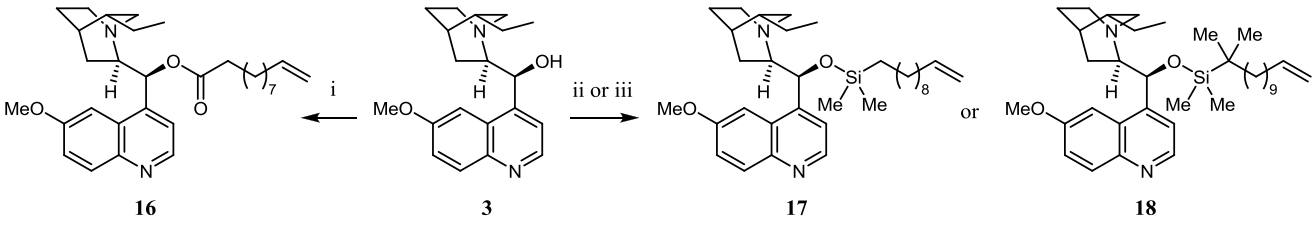
Preparation of anchorable DHQD derivatives

Cinchona alkaloids had been coupled to linear poly(methylhydrosiloxane) (PMHS) by the groups of Siegel and Bergbreiter.[10] However, the main goal of these investigations was the preparation of soluble materials, some of which were obtained by direct hydrosilylation of the alkaloid's 10,11-double bond. By contrast, the cross-linked structure of the IPB materials explored in the present work suggested the introduction of a spacer group between the chiral moiety and the terminal alkene-anchoring site. Similarly to Siegel and co-workers,[10a] synthetic efficiency considerations suggested to embed it into the 9-*O* substituent. This led to the design of the three DHQD derivatives **16**, **17**, and **18**, which can be considered the anchorable variants of the soluble Prop, TMS, or TBDMS organocatalysts noted above.

The synthesis of the silyl ethers **17** and **18** required the initial preparation of the corresponding chlorosilanes **13** and **15**, achieved as depicted in the Scheme 1 by reacting dichlorodimethylsilane with the Grignard reagents obtained from the halides **12** or **14**.[11] Besides using cheap chemicals, a practical advantage of this route was that pure-enough **13**, **14**, and **15** could be obtained in acceptable (yet not optimized) yields by a simple and scalable procedure that involved high-vacuum distillation as the purification technique.



Scheme 1. Synthesis of the chlorosilanes **13** and **15**. Reagents and conditions: (i) Mg, Et_2O; (ii) Me_2SiCl_2, THF, 50% from **12**; (iii)(a) acetone, Et_2O; (b) 37% HCl, $ZnCl_2$, 50% from **12**; (iv)(a) Mg, THF, 70°C; (b) Me_2SiCl_2, cat. CuCN, THF, 43% from **14**.



Scheme 2. Synthesis of the anchorable alkaloid derivatives **16**, **17**, and **18**. Reagents and conditions: (i) 1.3 equiv. 10-undecenoyl chloride, CH_2Cl_2, r.t., 48 h, 75%; (ii) 1.3 equiv. **13**, 2 equiv. Et_3N, 30 mol% DMAP, DMF, r.t., 48 h, 62%; (iii) 1.3 equiv. **15**, 4.5 equiv. Et_3N, 10 mol% DMAP, DMF, r.t., 72 h, 53%.

Next, the synthesis of the anchorable alkaloid derivatives was carried out as shown in the Scheme 2. For the preparation of the 9-*O* undecenoic ester **16** a modification of the reported procedure for the analogous Prop derivative was used,[7a] consisting in the reaction of DHQD (**3**) with commercially available 10-undecenoyl chloride without any additional base. Similarly, **17** and **18** were prepared by reacting **3** with the chlorosilanes **13** and **15** under the conditions reported for the synthesis of the corresponding TMS and TBDMS ethers.[7a,12] After chromatographic purification, fractions of **16**, **17**, and **18** were obtained in fair to good yields, as clear oils that gave a single spot by TLC. The identities of the three alkaloid derivatives were confirmed by electrospray mass spectrometry and by ^{1}H and ^{13}C NMR. In the case of the known ester **16** the spectroscopic constants proved identical to the published ones,[10a] including the occurrence of single sets of sharp resonances in both ^{1}H and ^{13}C NMR. On the contrary, the spectra of the new silyl ether **18** were somewhat more complicated, showing two distinct sets of sharp resonances (ratio ~ 76 : 24) in ^{1}H and ^{13}C NMR. Given the sample homogeneity, these observations are best explained as a consequence of the restricted rotation around the C_9-O and O-Si bonds of the hindered derivative **18**. Interestingly, similar conclusions were reported for other *Cinchona* alkaloid TBDMS silylethers, which showed a ~ 75 : 25 ratio of rotamers by ^{1}H NMR.[12]

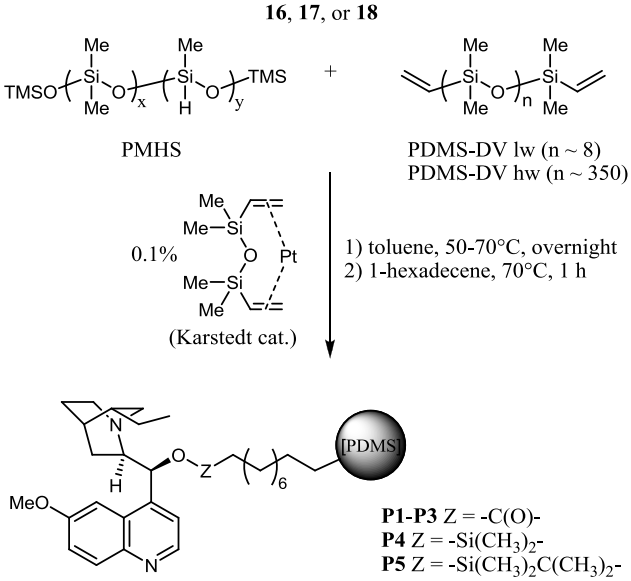
Preparation of DHQD derivatives in cross-linked silicone elastomeric films

Previous work in the immobilization of chelating Box ligands within elastomeric silicone films demonstrated the advantage of using highly active nanostructured solvated Pt catalysts in the hydrosilylation step.[8] However, the reduced coordinating ability of the monomeric derivatives **16-18**, as well as literature precedents,[10a] suggested that commercial Pt catalysts could also fit the needs of the present work.

To test this hypothesis, **17** was reacted in C_6D_6 with PMHS (x = y ~ 6, see Scheme 3), in the presence of a small amount of the commercial Karstedt catalyst (Si-H : **17** : Pt = 1000 : 200 : 1). After 5 h at 50°C, ^{1}H and ^{13}C NMR indicated a complete conversion, as evidenced by the disappearance of the olefin and allyl signals of the alkaloid's side chain. In addition, the spectra of the final solution showed neither degradation of the alkaloid core, nor significant isomerisation of the terminal double bond of **17** to the hydrosilylation-refractory internal positions.[13] The covalent linking of the chiral unit to PMHS was also confirmed by the growth in the ^{13}C spectrum of two broad resonances at 23.4 and 17.9 ppm that, by comparison with literature values,[14] identified the CH_2CH_2Si fragment of the polymer-bound alkaloid.

Whilst these initial experiments proved useful in validating the chemistry involved in the anchoring procedure, gelation and some gas evolution was noticed in the C_6D_6 sample shortly after the end of the NMR measurements. The poor solubility of the gelled material hampered a detailed investigation of the phenomenon, which was nonetheless likely to arise from side-reactions of the excess Si-H units of PMHS after the complete conversion of the vinyl groups of **17**.[13,15]

Because the observed phase separation made unfeasible the preparation of uniform elastomeric films by the previously developed two-step approach,[8] the investigation of a single-step procedure was decided instead. Toluene solutions of **16**, **17**, or **18**, PMHS, low and high molecular-weight divinyl-terminated silicones (PDMS-DV lw and hw, respectively)[8] and the Karstedt catalyst were hence gently heated overnight under air, in a PTFE-lined vessel (Scheme 3).



Scheme 3. Preparation of the IPB alkaloid derivatives **P1-P5**.

Table 1. Feed composition and characterization data for **P1-P5**.

Feed			Elastomeric film	
Alkaloid deriv.	PMHS [x : y]	Composition[a]		Loading [mmol g^{-1}][b]
16	6 : 6	3 : 1 : 1 (25)	**P1**	0.28±0.007
16	6 : 6	5 : 1 : 2 (30)	**P2**	0.19±0.004
16	0 : 26	3 : 1 : 1 (35)	**P3**	0.57±0.004
17	6 : 6	3 : 1 : 1 (25)	**P4**	0.24±0.007
18	6 : 6	3 : 1 : 1 (25)	**P5**	0.26±0.04

[a] Molar ratio Si-H : alkaloid deriv. : PDMS-DV lw (in parentheses wt% of PDMS-DV hw in the feed). [b] Alkaloid content from nitrogen elemental analysis (average of two determinations).

The evaporation of the solvent resulted in the casting of robust cross-linked films that were swollen with an excess of 1-hexadecene in toluene and heated again to cap any residual Si-H group. Continuous extraction with THF and CH_2Cl_2 and drying under vacuum afforded the five material **P1**-**P5** (Table 1) that were characterized by IR (Supporting Information) and microanalytical determination of the nitrogen content. The former technique ruled out significant amounts of unreacted Si-H and C=C units as demonstrated by the lack of appreciable absorptions at 2280-2400 cm^{-1} and ~1600 cm^{-1}, respectively, in all of the IPB materials.[16] In the case of **P1**, **P2**, and **P3** the incorporation of the ester derivative in the elastomeric network was also confirmed by the presence of a weak carbonyl stretching around 1748 cm^{-1}. IR spectroscopy proved less informative for **P4** and **P5** due to the lack of strong bands of the alkaloid and side-chain fragments in the spectral regions not obscured by the polysiloxane backbone. Nonetheless, nitrogen elemental analysis demonstrated a substantial incorporation of the chiral derivative for all of the prepared materials, with alkaloid contents ranging from 0.19 to 0.57 mmol g^{-1} (Table 1). The comparison of the experimental loadings with the values calculated from the feed compositions revealed that the functionalization degree of the recovered films **P1**-**P5** was more sensitive to the Si-H content of the PMHS precursor and Si-H : alkaloid ratio than to the actual nature of the chiral derivative. Indeed, the use of different soluble precursors (**16**, **17**, or **18**) but the same Si-H : alkaloid molar ratio (3 : 1) and PMHS copolymer (x = y ~ 6) in the preparation of **P1**, **P4**, and **P5** resulted in rather similar anchoring levels (60, 55, and 59% of the corresponding theoretical values, respectively). On the contrary, the increase of the Si-H : alkaloid ratio to 5 : 1 or the switch to the use of pure methylhydrosiloxane homopolymer (x = 0, y ~26) caused a significant rise of the incorporation of the same chiral derivative (**16**) in the materials **P2** and **P3** (76 and 129% of the theoretical, respectively).

Clearly, the attainment of a higher than expected loading for the latter was due to a significantly reduced incorporation of polysiloxane components in the film. This conclusion was confirmed by the mass recovery of purified insoluble materials that proved much lower for **P3** than for the other cross-linked films (22% vs. 74-90% of the feed weight, respectively). Together with the trends in the functionalization degree, discussed above, these results affected also the absolute immobilization yield of the alkaloid precursor **16**, **17**, or **18** that was 28% in the case of **P3** and 45-56% for the other IPB systems **P1**, **P2**, **P4**, or **P5**.

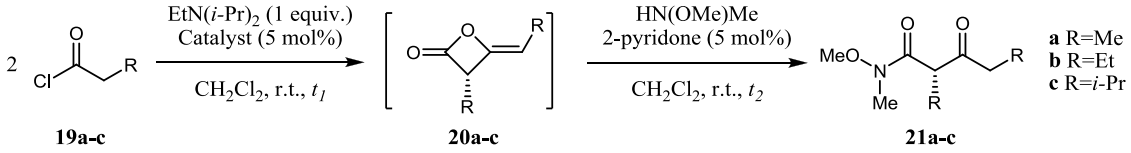
Homogeneous asymmetric ketene dimerization

To test the suitability of the new chiral derivatives of this work in the asymmetric dimerization of ketenes, some homogeneous catalysis experiments were carried out first. With this aim, the soluble compounds **16**, **17**, and **18** were employed under the conditions described by Calter and co-workers for the in situ generation of ketenes from the acid chlorides **19a-c** and one-pot opening of the intermediate β-lactone dimers **20a-c** to the corresponding Weinreb amides **21a-c** (see also the Supporting Information).[7f]

In the dimerization of methylketene from **19a** (Table 2, entries 1, 4, and 5) all of the three modified catalysts **16**, **17**, and **18** appeared capable of providing **21a** with 94-98% *ee*, albeit in slightly reduced yields (56-64%) with respect to the published ones (65-79%).[7f] Interestingly, in the case of **17** the enantioselectivity level matched that reported for the corresponding TMS ether of quinidine (TMS-**1**), thus suggesting that neither the introduction of the longer side chain in the silyl group nor the saturation of the alkaloid 10,11-double bond had major impact on the reaction stereoselectivity.

A similar comparison for the other two organocatalysts is less straightforward because published data refer to the use of Prop or TBDMS derivatives of the quinine pseudoenantiomer (**2**) that afford 69% *ee* and 94% *ee*, respectively, in the dimerization of the ketene from the acid chloride **19a**.[7f]

Table 2. Homogeneous and heterogeneous asymmetric catalytic dimerization of ketenes from acid chlorides.



19a-c **20a-c** **21a-c**

Run	Catalyst	Acid chloride	t_1 [h]	t_2 [h]	Product	Yield [%][a]	Ee [%][b]
1	**16**	**19a**	6	2	**21a**	57	94
2	**16**	**19b**	6	2	**21b**	83	96
3	**16**	**19c**	24	24	**21c**	52	97
4	**17**	**19a**	6	2	**21a**	56	97
5	**18**	**19a**	6	2	**21a**	64	98
6	**P1**	**19a**	6	2	**21a**	58	94
7	**P1**	**19b**	6	2	**21b**	88	96
8	**P1**	**19c**	24	24	**21c**	79	95
9	**P2**	**19a**	6	2	**21a**	60	95
10	**P3**	**19a**	6	2	**21a**	64	93
11	**P4**	**19a**	6	2	**21a**	53	94
12	**P4**	**19b**	6	2	**21b**	69	99
13	**P4**	**19c**	24	24	**21c**	67	99
14	**P5**	**19a**	6	2	**21a**	57	98
15	**P5**	**19b**	6	2	**21b**	62	95
16	**P5**	**19c**	24	24	**21c**	50	96

[a] After isolation by flash chromatography. [b] By HPLC with chiral stationary phases; the prevailing enantiomer had (*S*) configuration.

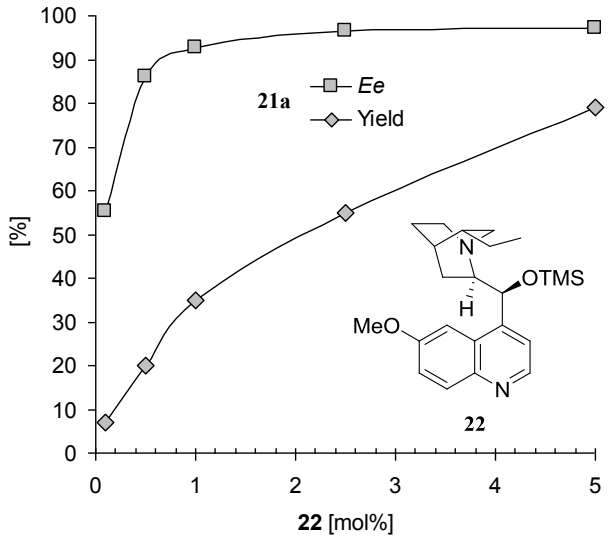


Figure 3. Asymmetric dimerization of methylketene in the presence of the soluble derivative **22** (5 mol% data are for TMS-**2**, from ref.[7f]; for the other conditions see Table 2).

Nonetheless, we were pleased to find that **16** and **18** could provide 94% *ee* and 98% *ee*, respectively, in the same reaction (Table 2, entries 1 and 5). Besides witnessing the strong influence of the alkaloid peripheral positions, including the diastereomeric relationship between the chiral cores,[17] the practical implication of these findings was the possibility of attaining synthetically useful *ee* values in the quinidine series by the use of the simple ester derivative **16**. This conclusion was corroborated by two further runs with **16** in the dimerization of homologous ketenes from **19b** and **19c**, which led to the corresponding Weinreb amides with 96-97% *ee* (Table 2, entries 2 and 3).

For a better comparison of the productivity of homogeneous and heterogeneous catalytic systems (vide infra), a series of experiments were also carried out with variable amounts of the soluble TMS ether **22** (Figure 3). The results of these tests revealed that the reaction of methylketene could tolerate a twofold reduction of the catalyst loading below the literature conditions (5 mol%)[7f] without any major erosion of the *ee* of the product **21a**. However, further lowering of the alkaloid amount resulted in a rapid degradation of performances, with an abrupt decrease of isolated yields and *ee* values when the loading was reduced below the 1 mol% level.

Heterogeneous asymmetric ketene dimerization

The heterogeneous catalysis experiments were carried out with 5 mol% of the IPB derivatives **P1**-**P5**. The conditions were the same as described above for the homogeneous runs with the only variant that, due to the lack of an active role of the alkaloid units in the opening of the chiral β-lactone intermediate,[7b] the successive reaction steps were performed in two distinct vessels. As detailed elsewhere,[5g] after stirring for the time t_1 the solution containing the chiral dimer **20a-c** was separated from the organocatalyst film by siphoning, treated with *N,O*-dimethylhydroxylamine and 2-pyridone and then stirred again for the time t_2 to give the final product **21a-c**. Standard filtration experiments were carried out concurrently (Supporting Information) and ruled out a significant homogeneous contribution to catalysis from species leached into the solution.

Screening of **P1**-**P5** in the reaction of propionyl chloride (**19a**) showed that all of the silicone-supported derivatives could effectively promote the asymmetric dimerization of methylketene (Table 2, entries 6, 9-10, and 14). Despite the insoluble nature of the catalytic system, the isolated yields of the chiral dipropionate product **21a** proved satisfactory and comparable to those afforded by the soluble compounds **16**-**18** after identical t_1 and t_2 reaction times. Excellent results were also achieved in terms of enantioselectivity, with *ee* values as high as 93-98%. As expected on the basis of the preliminary homogeneous runs, the stereochemical efficiency of the supported organocatalysts turned out to be somewhat dependant on the structure of the immobilized alkaloid derivative, reaching optimal results in the case of the TBDMS-like material **P5** (Table 2, entry 14). On the contrary, different film composition and catalysts loading appeared to have a minor impact on the catalytic properties, as proved by the rather uniform performances of the materials containing the same undecenoyl ester derivative within the variable polymer architecture of **P1**-**P3** (Table 2, entries 6, 9, and 10).

The promising results in the asymmetric dimerization of methylketene were confirmed by using **P1**, **P4**, and **P5** in the reaction of the homologues from the acid chlorides **19b** and **19c** (Table 2, entries 7, 8, 12, 13, 15, and 16). Also in these cases acceptable yields were obtained under standard conditions together with *ee* values matching, or slightly surpassing, those afforded by the soluble alkaloid derivatives in this work (Table 2, entries 2 and 3) or from the literature.[7f]

Overall, the covalent immobilization into elastomeric silicone films proved capable of preserving to a large extent the high enantioselectivity and satisfactory activity of the soluble organocatalysts **16**-**18**. Therefore, the cross-linked polysiloxane network of **P1**-**P5** appears well suited for the heterogeneous catalysis of the reaction under exam, with no appreciable impact on the asymmetric induction ability of the supported chiral units and the possibility for the species in solution to access them. Concerning this latter point, it is interesting to note that even if the rate-limiting step in the homogeneous reaction -ketene formation- is known to be independent from the alkaloid derivative concentration,[7f] the attainment of dimerization products with substantial yields and *ee* values requires the involvement of the chiral organocatalyst For this reason, the occurrence of critical diffusion problems in the materials **P1**-**P5** appears unlikely.

Catalyst recycling and productivity evaluation

As already found with Box ligands,[8] the film shape of the materials **P1**-**P5** allowed their prompt separation from the reaction mixture by siphoning. This feature greatly facilitated the study of recycling that was evaluated by selecting the reaction of **19a** as the benchmark.

The experiments (Figure 4a) demonstrated that each of the IPB systems could promote at least five consecutive dimerization runs, still leading to the product **21a** with substantial *ee* values. Nonetheless, some significant differences were also noted in the propensity of the diverse material to retain their initial catalytic efficiency on recycling. In particular, while the ester-type systems **P1**-**P3** underwent a rather fast drop of performances in the successive runs (28-33% yield, 79-83% *ee* in the 5th cycle; yield data not shown in Figure 4), the silyl ether materials **P4** and **P5** continued to provide nearly unchanged results in this short reaction series (45-55% yield, 94-95% *ee* in the 5th cycle).

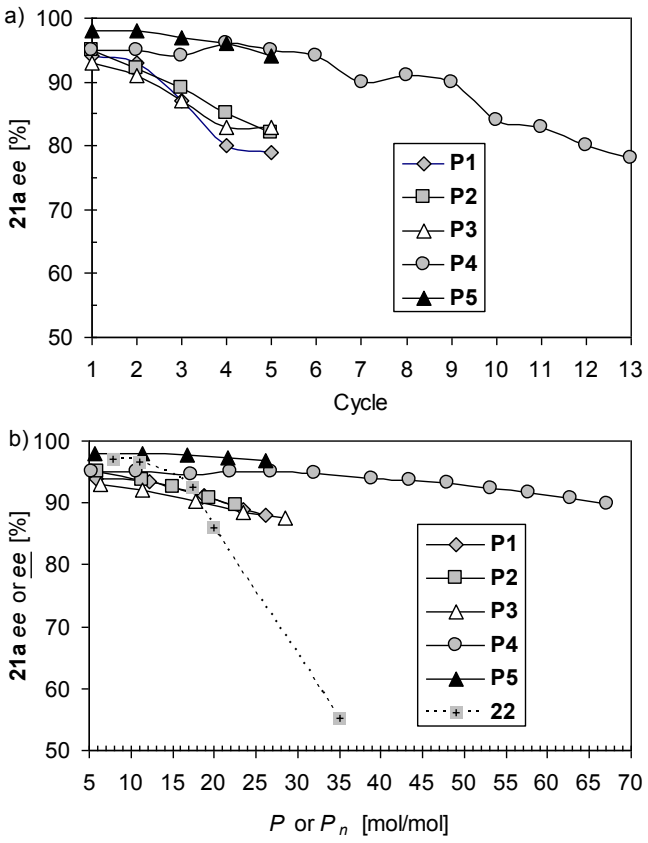


Figure 4. a) *Ee* of the product **21a** in the recycle runs of **P1**-**P5** (for the conditions, see Table 2; **21a** was obtained in 28-65% isolated yield); *b*) Enantioselectivity *vs.* productivity for soluble (**22**) and IPB (**P1**-**P5**) catalysts (for the meaning of *P*, P_n, and ee, see the text).

Because the preparation of **P4** requires a more convenient soluble precursor than for **P5**, the former material was selected for further testing. With this aim, eight more runs were performed with the used film to give the additional data included in the Figure 4a. The results of these experiments showed that the IPB organocatalyst could be employed in thirteen successive cycles, still providing **21a** in 45% isolated yield (data not shown) even in the last run. Concerning the enantioselectivity, a moderate negative trend was observed after the 6th cycle, which nevertheless did not preclude the attainment of 90-91% *ee* in the following three and 79% *ee* in the final one.[18]

Although the repeated use of **P4** appears capable of improving the organocatalyst productivity over the analogous homogeneous systems, as discussed in the Introduction the assessment of this aspect cannot be disjoint from the concurrent evaluation of the enantioselectivity attained under alternative conditions. For this reason, the available data from the benchmark homogeneous and heterogeneous methylketene dimerization runs were converted into *P@ee* value pairs[5g] and, for the sake of comparison, plotted in an enantioselectivity vs. productivity (*ee-P*) graph (Figure 4b).

As far as the homogeneous reactions with **22** are concerned, the *P@ee* points were directly calculated from the catalyst amount employed in each run and the recorded yield and *ee* of the product **21a** (Figure 3). The outcome of this analysis, shown as the broken curve in the Figure 4b, revealed that the use of 2.5 mol% of the soluble derivative **22** could afford a result (*P*~11@97% *ee*), which compares favourably with that attained under standard literature conditions (*e.g. P*~8@97% *ee* from the published data with 5 mol% of TMS-**2**).[7f] However, due to the anticipated relationship between alkaloid amount and catalytic performances (Figure 3) this favourable trend did not keep valid on moving to the low-end region of catalyst loading. In this respect it is worth noting that, besides the enantioselectivity reduction, the relatively large *P* values scored by the use of 0.1 mol% of **22** (*P*~35@55% *ee*) actually correspond to the isolation of impractically small amounts of the product **21a** (7% yield). Accordingly, in the reaction under exam a moderate reduction of the catalyst loading appears to be a viable option for increasing the productivity of the alkaloid derivative, which however cannot be pursued much below the 1 mol% threshold (where *P*~17@93% *ee*, 35% isolated yield was obtained).

The establishment of the *ee-P* relationship for the soluble catalyst set the stage for a better assessment of the IPB materials **P1**-**P5**. For this purpose, *ee* and yield data of the heterogeneous runs were converted into P_n@ee pairs, defined as the productivity (P_n) and weight-averaged enantiomeric excess (ee) for a virtual gross-sample of **21a** obtained by ideally pooling together those isolated up to the *n*-th run (for details, see the Supporting Information).

Examination of the results shown as solid curves in the Figure 4b revealed that two limiting scenarios had to be considered, depending on whether the priority was given to the maximization of the product's *ee* or to the catalyst's productivity. With the former choice, **P5** was the only IPB system that could rival with the homogeneous catalysts across a number of reaction cycles. Even though a complete *ee-P* analysis for the TBDMS soluble system was not performed in this work, the P_5 ~26@97% ee reached with **P5** (Figure 4b) appears substantially superior to *P*~6@97% *ee* and *P*~7@94% *ee* provided under standard conditions by the soluble derivatives **18** (Table 2, entry 5) and TBDMS-**1**,[7f] respectively.

In order to make a comparison in the alternative situation, i.e. when some reduction of the enantioselectivity was deemed acceptable, the average enantiomeric purity scored at the end of the cycles with **P4** (90% ee) was arbitrarily selected as the reference level. With this choice the interpolation of the data for the soluble organocatalyst (Figure 4b) led to an estimation of *P*~18@90% *ee*, corresponding to the use of ~0.75 mol% of **22** (see Figure 3); by contrast, the cumulative productivity of the heterogeneous system could be directly obtained as the rightmost point of the corresponding curve and was P_{13}~67@90% ee.

Comparison of these results clearly demonstrated that the recycling of the IPB system **P4** was capable of affording nearly three times more product than the soluble derivative **22** at reduced loadings, the amount of chiral organocatalyst and the enantiomeric purity of the final amide **21a** being the same. Interestingly, this perhaps unimpressive *P* increase was not the only advantage of the IPB approach because the use of the supported system also allowed to isolate the stereochemically labile product **21a** in a nearly pure form, without the need of any chromatographic purification, and with a substantially higher yield (51% overall) than with the soluble organocatalyst at low loadings (~27% yield, see Figure 3).

In the depicted scenario, the choice of immobilizing the chiral organocatalyst proved hence more effective than the mere reduction of the loading of the corresponding soluble derivative, both in terms of larger productivity of the expensive alkaloid catalyst and better use of the other chemicals involved in the catalyzed reaction. This conclusion is obviously related to the disclosed features of the reactions under exam, which include a

reasonably good recycling profile for the IPB systems (especially **P4** and **P5**) as well as the specific response of the homogeneous process on lowering of the catalyst loading. Because neither of the two results could be easily predicted a priori, the significance of the *P@ee* analysis described above should be evident. In this respect it goes to say that this kind of analysis is not expected to be an universal criterion for deciding in favour of any of the two options in a real application perspective, as many other factors (*e.g.* preparation simplicity and cost of either system, turnover frequency, actual product' yield, etc.) could decisively come into play. Nonetheless, in all the cases like the present one, where the chiral catalyst is the largely most expensive chemical in the transformation under study, the evaluation of the *P@ee* / P_n@ee relationships for the homogeneous and heterogeneous cases may be of prime importance for a fair assessment of the relative merits of the two alternatives towards process intensification.[19]

As a final comment, it is worth noting that the polystyrene-supported dimeric systems **11** mentioned in the Introduction appear to provide superior results than the materials **P1**-**P5** in this study. In fact, the former IPB derivatives showed a significantly better recycling profile than the latter and allowed the attainment of significantly larger productivities, even in the high-end *ee* range (*e.g.* P_8 ~57@97% ee and P_{20} ~135@95% ee).[5g] For reasons that are unknown at present but possibly related to the different chemical stability of the linkage connecting the 9-*O* substituent with the chiral core, for the moment the polystyrene-supported dimeric systems **11** remain therefore the reference materials for the heterogeneous catalysis of the asymmetric dimerization of ketenes.

Conclusions

In summary, a convenient procedure has been described for the covalent immobilization of different ester or silyl ether monomeric derivatives of 10,11-dihydroquinidine into cross-linked insoluble films. In spite of the rather unconventional support structure, the IPB systems obtained by this approach proved highly enantioselective and reasonably recyclable organocatalysts in the heterogeneous asymmetric dimerization of ketenes. This allowed the preparation of chiral Weinreb β-ketoamides with 79-99% *ee*, in the course of up to 13 reaction cycles.

Moreover, the problem of a sound comparison between IPB systems and their homogeneous counterparts has been addressed by introducing a productivity/enantioselectivity protocol that, in essence, requires the extended re-use of the recoverable catalyst, on the one hand, and the evaluation of the corresponding homogeneous system at progressively lower loadings, on the other. Because this kind of analysis allows a better critical evaluation of the results than the customary description of (a few) recycle runs alone, we feel that the proposed procedure could become a standard tool for further studies in the field of recoverable enantioselective catalysts.

Given the straightforward preparation of the alkaloid monomeric precursors **16**-**18** and the suitability of hydrosilylation chemistry also for the covalent anchoring of organic derivatives and catalysts within capillary channels,[20] the extension to microfluidic devices of the approach described in this work is currently underway.

Experimental Section

For the materials, general methods, instrumentation, and analytical procedures, see the Supporting Information.

Chlorodimethyl(undec-10-enyl)silane (13).
A 100 mL three-necked flask fitted with a reflux condenser, dropping funnel, nitrogen inlet, and magnetic stirring bar was charged with degreased magnesium turnings (0.716 g, 29.4 mmol), dry diethyl ether (10 mL), and a crystal of iodine. The flask was wrapped with a tissue cloth and a solution of 11-bromoundec-1-ene (6.25 g, 26.8 mmol) in dry diethyl ether (15 mL) was added dropwise over 2 h to the rapidly stirred suspension, so as to maintain a slight but regular reflux in the condenser. The dropping funnel was rinsed with dry diethyl ether (3 mL) and the resulting mixture was left stirring overnight at r.t., to give a mid brown solution of the Grignard reagent that contained small amounts of unreacted magnesium and showed >98% GC conversion of the starting bromide. After settling of the solid, the clear supernatant and two THF rinses (4 mL) were cannulated under nitrogen into a second 100 mL three-necked flask containing a rapidly stirred solution of dichlorodimethylsilane (6.9 mL, 57 mmol, 2.1 equiv.) in dry THF (10 mL). The initially clear solution was left stirring overnight at r.t. under nitrogen, to give a thick white suspension which was diluted with dry *n*-hexane (20 mL) and filtered under nitrogen through a mid-porosity glass frit. The residue on the frit was washed with dry *n*-hexane (7×5 mL) and the combined filtrates were concentrated with a rotary evaporator. The crude compound was distilled under reduced pressure in a Claisen apparatus to give **13** as a clear colorless oil (*b.p.* 73-74°C/0.2 mmHg, 3.30 g, 50% yield). ^{1}H NMR (300 MHz, $CDCl_3$): δ= 0.40 (s, 6H), 0.69-0.94 (m, 2H), 1.13-1.57 (m, 14H), 1.90-2.17 (m, 2H), 4.84-5.10 (m, 2H), 5.81 (ddt, J_a = 16.9, J_b = 10.2, J_c = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ= 1.83, 19.17, 23.15, 29.12, 29.30, 29.40, 29.64, 29.67, 33.14, 33.99, 114.25, 139.29; elemental analysis calcd (%) for $C_{13}H_{27}ClSi$: C 63.24, H 11.02, Cl 14.36, Si, 11.38; found: C 63.20, H 11.00, Cl 14.65.

12-Chloro-12-methyltridec-1-ene (14).
A solution of undec-11-en-1-ylmagnesium bromide was prepared as detailed in the previous paragraph from magnesium turnings (0.912 g), 11-bromoundec-1-ene (8.00 g, 34.3 mmol), and dry diethyl ether (10+15 mL). After cooling externally with an ice bath, dry acetone (3.8 mL, 52 mmol, 1.5 eq) in diethyl ether (5 mL) was added dropwise over 1 h. The dropping funnel was washed with an ether rinse (5 mL) and, after stirring at r.t. for 15 min, the content of the flask was hydrolyzed with satd. ammonium chloride (25 mL). The organic components were extracted with diethyl ether (3×10 mL) and the combined organic phases dried over sodium sulfate. Removal of the volatiles with a rotary evaporator and then at 0.05 mmHg afforded crude 2-methyltridec-12-en-2-ol (7.10 g), as a clear pale-yellow oil that was directly used in the next step.
Crude 2-methyltridec-12-en-2-ol (5.00g) was placed into a 100 mL two-necked flask fitted with a dropping funnel and a magnetic stirring bar. After cooling externally with an ice bath, a solution of zinc chloride (6.42 g, 47 mmol) in 37% HCl (6.5 mL) was added dropwise over 40 min, with rapid stirring. The dropping funnel was rinsed with 37% HCl (3 mL) and the resulting orange mixture was warmed to r.t. and kept under vigorous stirring until consumption of the alcohol substrate by GC analysis (1 h). The content of the flask was diluted with water (15 mL) and extracted with light petroleum ether (3×15 mL). The organic phases were dried over calcium chloride and the volatiles removed with a rotary evaporator to give an oil. The crude product was purified by distillation at reduced pressure in a Claisen apparatus with a short Vigreux column. After discarding a forerun, the chloride **14** was obtained as a clear colorless oil (*b.p.* 106-115°C/0.15 mmHg, 3.45 g, 61% yield over two steps). ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.07-1.51 (m, 14H), 1.52 (s, 6H), 1.66-1.85 (m, 2H), 1.88-2.16 (m, 2H), 4.76-5.16 (m, 2H), 5.81 (ddt, J_a = 16.9, J_b = 10.1, J_c = 6.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= 25.26, 29.08, 29.27, 29.52, 29.68, 29.87, 32.54, 33.96, 46.25, 71.30, 114.25, 139.27; elemental analysis calcd (%) for $C_{14}H_{27}Cl$: C 72.85, H 11.79, Cl 15.36; found: C 73.01, H 11.82, Cl 15.28.

Chlorodimethyl(2-methylpent-4-en-2-yl)silane (15).

A 100 mL three-necked flask fitted with a reflux condenser, dropping funnel, nitrogen inlet, and magnetic stirring bar was charged with degreased magnesium turnings (0.330 g, 13.7 mmol) and dry THF (5 mL). After the addition of 1,2-dibromoethane (0.2 mL) the flask was placed into an oil bath at 90°C and a solution of the chloride **14** (2.61 g, 11.3 mmol) in dry THF (5 mL) was added dropwise over 2 h. The dropping funnel was rinsed with dry THF (3 mL) and the resulting dark solution was kept under stirring at 70°C for 4 h, whereupon >85% conversion of the halogen substrate was observed by GC. After settling of the small amount of residual magnesium, the clear supernatant and two THF rinses (2 mL) were cannulated under nitrogen into a second 100 mL three-necked flask containing a stirred solution of dichlorodimethylsilane (1.61 g, 12.4 mmol, 1.1 equiv.) and copper cyanide (15 mg, 0.24 mmol, 2 mol%) in dry THF (5 mL). The resulting brownish clear solution was left stirring under nitrogen for 24 h at 70°C. After cooling to r.t., the solution was diluted with dry *n*-hexane (30 mL) and filtered under nitrogen through a mid-porosity glass frit. The residue on the frit was washed with dry *n*-hexane (2×5 mL) and the combined filtrates were concentrated with a rotary evaporator. The crude compound was distilled under high vacuum in a Claisen apparatus connected with an oil diffusion pump. After discarding an abundant forerun, a fraction was collected (*b.p.* 40-73°C/3-6·10^{-5} mbar) that, by ^{1}H NMR and GC-ms, contained ~68 wt% of **15** together with 12-methyltridec-1-ene (~20 wt%) and minor amounts (<5 wt%) of 12-methyltridec-1,12-diene and the starting chloride **14**. The mixture (1.39 g, ~30% yield of the title compound) was directly used in the next step. ^{1}H NMR (200 MHz, $CDCl_3$): δ= 0.37 (s, 6H), 0.96 (s, 6H), 1.04-1.50 (m, 16H), 1.90-2.27 (m, 2H), 4.84-5.19 (m, 2H), 5.82 (ddt, J_a = 16.9, J_b =10.1, J_c = 6.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= -0.73, 22.28, 23.79, 29.01, 29.21, 29.57, 29.69, 29.77, 30.72, 33.88, 38.27, 114.14, 139.20; HRMS (EI+): m/z calcd for $C_{16}H_{33}ClSi$: 288.2040; found: 288.2047.

9-*O*-[Dimethyl(undec-10-en-1-yl)silyl]-10,11-dihydroquinidine (17).

A 10 mL Schlenk tube was charged under nitrogen with hydroquinidine (0.250 g, 0.766 mmol), dry DMF (1.0 mL), triethylamine (0.21 mL, 1.5 mmol), 4-dimethylaminopyridine (30 mg, 0.25 mmol, 30 mol%), and the chlorosilane **13** (0.28 g, 1.0 mmol, 1.3 eq). The resulting mixture was magnetically stirred at r.t. for 48 h and then diluted with toluene (5 mL). The organic phases were washed with water (2×5 mL) and dried over anhydrous sodium sulfate. The volatiles were removed with a rotary evaporator and the residue was purified by flash chromatography (SiO_2, AcOEt : MeOH = 95 : 5) to give **17** (0.255 g, 62% yield) as a pale-yellow viscous oil. TLC R_f = 0.51 (SiO_2, AcOEt:MeOH 95:5); $[\alpha]_D^{21}$ = +1.1 (c = 0.51 g/100mL, CH_2Cl_2); MS(ES+): *m/z* +537.8 ($M+H^+$); ^{1}H NMR (200 MHz, $CDCl_3$): δ= -0.03 (s, 3H), 0.08 (s, 3H), 0.53-0.55 (m, 2H), 0.90 (t, J = 7.1 Hz, 3H), 1.10-1.75 (m, 14H), 1.98-2.08 (m, 2H), 2.68-2.98 (m, 4H), 3.08-3.22 (m, 1H), 3.94 (s, 3H), 4.86-5.02 (m, 2H), 5.68-5.89 (m, 2H), 7.22 (br. s, 1H), 7.34 (dd, J_a = 9.2, J_b = 2.5 Hz, 1H), 7.51 (br. s, 1H), 7.99 (d, J = 9.0 Hz, 1H), 8.71 (d, J = 4.4 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ= -1.45, 12.08, 16.93, 19.69, 23.26, 25.32, 26.47, 27.16, 29.53, 29.57, 33.50, 33.87, 37.46, 50.55, 51.12, 55.96, 60.66, 73.06, 100.64, 114.15, 118.70, 121.79, 126.24, 131.87, 139.26, 144.50, 147.42, 147.65,158.11; elemental analysis calcd (%) for $C_{33}H_{52}N_2O_2Si$: C 73.83, H 9.76, N 5.22, O 5.96, Si 5.23, found: C 73.40, H 9.62, N 5.17.

9-*O*-[Dimethyl(2-methyltridec-12-en-2-yl)silyl]-10,11-dihydroquinidine (18).

A 10 mL Schlenk tube was charged under nitrogen with hydroquinidine (0.430 g, 1.32 mmol), dry DMF (1.0 mL), triethylamine (0.83 mL, 6.0 mmol), 4-dimethylaminopyridine (16 mg, 0.13 mmol, 10 mol%), and the chlorosilane **15** (0.66 g, 68% purity, ~1.5 mmol, 1.1 eq). The resulting mixture was magnetically stirred at r.t. for 72 h and then diluted with toluene (5 mL). The organic phases were washed with water (2×5 mL) and dried over sodium sulfate. The volatiles were removed with a rotary evaporator and the residue was purified by flash chromatography (SiO_2, AcOEt : MeOH = 95 : 5) to give **18** (0.406 g, 53% yield) as a pale-yellow viscous oil. TLC R_f = 0.59 (SiO_2, AcOEt:MeOH 95:5); $[\alpha]_D^{21}$ = +1.0 (c = 0.53 g/100mL, $CHCl_3$); MS(ES+): *m/z* +579.9 ($M+H^+$); ^{1}H NMR (600 MHz,$CDCl_3$): δ(*major rotamer*, ~76%)= -0.33 (s, 3H), 0.15 (s, 3H), 0.90 (t, J = 7.4 Hz, 3H), 0.92 (s, 3H), 0.94 (s, 3H), 0.99–1.58 (m, 21H), 1.64 (br. s, 1H), 1.72 (m, 1H), 1.92–2.10 (m, 3H), 2.65–2.75 (m, 1H), 2.76–2.94 (m, 3H), 2.96–3.03 (m, 1H), 3.94 (s, 3H), 4.89–5.02 (m, 2H), 5.60 (d, J = 3.1 Hz, 1H), 5.81 (ddt, J_a = 16.9, J_b = 10.2, J_c = 6.7 Hz, 1H), 7.19 (d, J = 2.4 Hz, 1H), 7.36 (dd, J_a = 9.2, J_b = 2.6 Hz, 1H), 7.55 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 8.73 (d, J = 4.5 Hz, 1H); δ(*minor rotamer*, ~24%)= -0.42 (s, 3H), 0.11 (s, 3H), 0.80 (s, 3H), 0.82 (s, 3H) 2.45–2.53 (m, 2H), 2.55–2.64 (m, 1H), 3.35–3.49 (m, 1H), 3.92 (s, 3H), 4.80 (d, J = 9.2 Hz, 1H), 7.10 (d, J = 4.3 Hz, 1H), 7.32 (dd, J_a = 9.2, J_b = 2.7 Hz, 1H), 7.86 (d, J = 2.7 Hz, 1H), 7.98 (d, J = 9.2 Hz, 1H), 8.64 (d, J = 4.2 Hz, 1H); ^{13}C-NMR (50 MHz, $CDCl_3$): δ(*major* + *minor rotamer*)= -4.29, -4.05, -3.89, -3.75, 12.18, 20.65, 21.23, 21.40, 22.86, 22.91, 23.81, 23.98, 25.28, 25.88, 26.24, 26.31, 26.62, 27.29, 27.56, 29.04, 29.26, 29.62, 29.79, 29.85, 30.89, 33.92, 37.71, 38.76, 38.86, 49.62, 49.92, 50.55, 51.49, 55.45, 55.80, 61.05, 61.15, 73.15, 79.64, 100.51, 105.00, 114.19, 119.03, 121.26, 121.41, 121.67, 126.40, 127.13, 131.53, 131.95, 139.30, 144.40, 145.53, 147.46, 147.59, 148.42, 156.57, 157.96; elemental analysis calcd (%) for $C_{36}H_{58}N_2O_2Si$·0.02 CH_2Cl_2: C 74.51, H 10.07, Cl 0.24, N 4.82, O 5.51, Si 4.84; found: C 74.59, H 10.15, N 4.81.

Preparation of P1-P5 by anchoring 16-18 into cross-linked silicone films. General procedure.

A solution of the unsaturated alkaloid derivative **16**, **17**, or **18** (0.40-0.75 mmol), PMHS, PDMS-DV lw, and PDMS-DV hw (for the exact ratios, see Table 1) in toluene (14-20 mL) was poured into a flat PTFE-lined vessel (90-150 cm^2 bottom area). A 1.0 mM solution of the Karstedt catalyst in toluene (molar ratio SiH/Pt = 1000) was evenly added drop by drop and, after swirling to complete the mixing of the solutions, the vessel was covered with a glass lid and heated under air for 1 h, on a plate set at 50° C. The temperature was then raised to 70°C to effect the solvent evaporation and polymer cross-linking. After overnight curing, the resulting solid film was swollen with a solution of 1-hexadecene (0.10 mL) in toluene (10 mL) and the volatiles were evaporated again by gently heating for 1 h at 70°C. The polymer film was moistened with little THF to facilitate the detachment from the vessel and transferred to a metal-net thimble, which was placed into a Kumagawa device. After continuous extraction over 2 days, first with dry THF and then with dry CH_2Cl_2, the almost colourless and nearly transparent material **P1-P5** (Figure S1) was dried under reduced pressure (0.05 mmHg) Callipers measurement of the resulting soft, elastic films indicated an approximate thickness of 0.2 mm. The material was characterized by IR (Figure S2) and elemental analysis. Elemental analysis found (N%): **P1** 0.77, **P2** 0.53, **P3** 1.59, **P4** 0.66, **P5** 0.73.

Heterogeneous catalytic asymmetric ketene dimerization. General procedure.

A 50 mL Schlenk tube, provided with a magnetic follower and stopcock side arm, was charged under nitrogen with **P1-P5** (88-263 mg, corresponding 0.050 mmol, 5 mol%, of the supported alkaloid derivative). After sealing the tube with a septum, dry CH_2Cl_2 (10 mL) was syringed into the tube and the polymer film allowed to swell by stirring for 5 min. *N,N*-Diisopropylethylamine (170 μL, 1.0 mmol) and acid chloride **19a-c** (1.0 mmol) were sequentially injected through the septum and the mixture was set stirring at 500 rpm at r.t. After the time t_1 (Table 2), the clear supernatant was cannulated under nitrogen into a dry Schlenk tube and the polymer film washed with CH_2Cl_2 (5 mL). The combined organic phases were treated with HN(OMe)Me (37 μL, 0.50 mmol) and 2-pyridone (4.7 mg, 0.05 mmol) and the resulting solution was stirred at room temperature

for the time t_2 (Table 2). For the *ee* determination, a sample of the reaction mixture (0.20 mL) was passed through small pad of silica gel with *n*-hexane : AcOEt = 2 : 1 (3×1 mL), evaporated with a nitrogen flow and dissolved in 2-propanol for HPLC analysis.[5g,7f] The remaining of the solution was washed with concentrated pH 7 buffer solution,[7f] dried (Na_2SO_4), and evaporated to give the Weinreb amides **21a-c** as turbid oils that were nearly pure by ^{1}H NMR (Figure S3). The polymeric film recovered after cannulation was washed with dry CH_2Cl_2 (2×1 mL) and then directly used in further catalysis cycles.

Supporting Information (see footnote on the first page of this article): Procedure for the homogeneous catalysis runs, spectra of the new compounds, appearance and IR of the polymer films, and elaboration of the *P/ee* data.

Acknowledgments

Work supported by the University of Pisa, MIUR (Project "Sintesi e Stereocontrollo di Molecole Organiche per lo Sviluppo di Metodologie Innovative di Interesse Applicativo - PRIN 2007") and ICCOM-CNR.

[1] a) *Chiral Catalyst Immobilization and Recycling* (Eds.: D. E. De Vos, I. F. J. Vankelecom, P. A. Jacobs), Wiley-VCH, Weinheim, **2000**; b) Q.-H. Fan, Y.-M. Li, A. S. C. Chan, *Chem. Rev.* **2002**, *102*, 3385-3466; c) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401-3429; d) F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367-1390; e) M. Benaglia, *New J. Chem.* **2006**, *30*, 1525-1533; f) A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 418-514; g) J. Lu, P. H. Toy, *Chem. Rev.* **2009**, *109*, 815-838; h) T. E. Kristensen, T. Hansen, *Eur. J. Org. Chem.* **2010**, 3179-3204; i) *Heterogenized Homogeneous Catalysts for Fine Chemicals Production, Vol. 33* (Eds.: P. Barbaro, F. Liguori), Springer Netherlands, Dordrecht, **2010**; j) *Catalytic Methods in Asymmetric Synthesis* (Eds.: E. Gruttadauria, F. Giacalone), John Wiley & Sons, Inc., **2011**.

[2] a) O. Gleeson, R. Tekoriute, Y. K. Gun'ko, S. J. Connon, *Chem.--Eur. J.* **2009**, *15*, 5669-5673; b) C. W. Jones, *Top. Catal.* **2010**, *53*, 942-952.

[3] A. Mandoli, D. Pini, M. Fiori, P. Salvadori, *Eur. J. Org. Chem.* **2005**, 1271-1282.

[4] a) K. Kacprzak, J. Gawronski, *Synthesis* **2001**, 961-998; b) C. Palomo, M. Oiarbide, R. Lopez, *Chem. Soc. Rev.* **2009**, *38*, 632-653; c) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, *2010*, 1229,1279.

[5] a) C. E. Song, J. W. Yang, H.-J. Ha, *Tetrahedron: Asymm.* **1997**, *8*, 841-844; b) C. Bolm, A. Maischak, *Synlett* **2001**, 93-95; c) F. Bigi, S. Carloni, R. Maggi, A. Mazzacani, G. Sartori, G. Tanzi, *J. Mol. Catal. A: Chem.* **2002**, *182-183*, 533-539; d) S. France, D. Bernstein, A. Weatherwax, T. Lectka, *Org. Lett.* **2005**, *7*, 3009-3012; e) B. Thierry, J.-C. Plaquevent, D. Cahard, *Mol. Diversity* **2005**, *9*, 277-290; f) R. Chinchilla, C. Najera, F. J. Ortega, S. Tari, *Tetrahedron: Asymm.* **2009**, *20*, 2279-2286; g) R. P. Jumde, A. Mandoli, F. De Lorenzi, D. Pini, P. Salvadori, *Adv. Synth. Catal.* **2010**, *352*, 1434-1440.

[6] K. M. Kacprzak, N. M. Maier, W. Lindner, *Tetrahedron Lett.* **2006**, *47*, 8721-8726.

[7] a) M. A. Calter, *J. Org. Chem.* **1996**, *61*, 8006-8007; b) M. A. Calter, X. Guo, *J. Org. Chem.* **1998**, *63*, 5308-5309; c) M. A. Calter, F. C. Bi, *Org. Lett.* **2000**, *2*, 1529-1531; d) M. A. Calter, X. Guo, W. Liao, *Org. Lett.* **2001**, *3*, 1499-1501; e) M. A. Calter, X. Guo, *Tetrahedron* **2002**, *58*, 7093-7100; f) M. A. Calter, R. K. Orr, W. Song, *Org. Lett.* **2003**, *5*, 4745-4748.

[8] A. Mandoli, M. Lessi, D. Pini, C. Evangelisti, P. Salvadori, *Adv. Synth. Catal.* **2008**, *350*, 375-379.

[9] Y. Motoyama, T. Nishikata, H. Nagashima, *Chem.--Asian J.* **2011**, *6*, 78-82.

[10] a) M. S. DeClue, J. S. Siegel, *Org. Biomol. Chem.* **2004**, *2*, 2287-2298; b) M. A. Grunlan, K. R. Regan, D. E. Bergbreiter, *Chem. Commun.* **2006**, 1715-1717.

[11] a) A. Shirahata, *Tetrahedron Lett.* **1989**, *30*, 6393-6394; b) C. G. L. Khoo, J. B. Lando, H. Ishida, *J. Polym. Sci., Part B: Polym. Phys.* **1990**, *28*, 213-232.

[12] a) S. J. Rowan, J. K. M. Sanders, *J. Org. Chem.* **1998**, *63*, 1536-1546; b) S. J. Rowan, D. J. Reynolds, J. K. M. Sanders, *J. Org. Chem.* **1999**, *64*, 5804-5814.

[13] M. Butts, J. Cella, C. D. Wood, G. Gillette, R. Kerboua, J. Leman, L. Lewis, S. Rubinsztajn, F. Schattenmann, J. Stein, D. Wicht, S. Rajaraman, J. Wengrovius, in *Kirk-Othmer Encyclopedia of Chemical Technology (5th Edition), Vol. 22*, **2006**, pp. 547-626.

[14] B. P. S. Chauhan, J. S. Rathore, *J. Am. Chem. Soc.* **2005**, *127*, 13738-13738.

[15] J. Y. Corey, *Adv. Organomet. Chem.* **2004**, *51*, 1-52.

[16] P. L. Launer, in *Silicone Compounds Register and Review* (Ed.: B. Arkles), Petrarch Systems, Inc., Bristol, PA, **1987**available at http://www.gelest.com/Library/11Infra.pdf (access effected on Jun, 1st 2011).

[17] a) L. Mink, Z. Ma, R. A. Olsen, J. N. James, D. S. Sholl, L. J. Mueller, F. Zaera, *Top. Catal.* **2008**, *48*, 120-127; b) J. Lai, Z. Ma, L. Mink, L. J. Mueller, F. Zaera, *J. Phys. Chem. B* **2009**, *113*, 11696-11701.

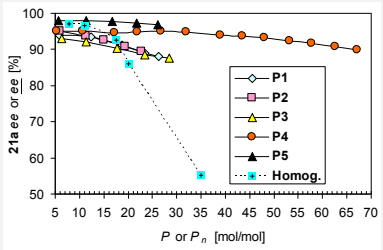
[18] In response to a referee query, it has be noted that rapid magnetic stirring caused some breaking of the polymer films into smaller particles. Even in the last cycle this problem did not prevent, however, the rapid separation of the reaction mixture by siphoning.

[19] For the sake of completeness, it should be noted that Calter and co-workers described conditions for the homogeneous dimerization which provide up to P ~ 92@99% ee (Ref. 7d). However, these protocols require the external generation of methylketene and the use of low temperatures (-78°C) and are, therefore, less convenient than the alternative procedure also followed in this work.

[20] a) O. Trapp, S. K. Weber, S. Bauch, W. Hofstadt, *Angew. Chem., Int. Ed.* **2007**, *46*, 7307-7310; b) D. Wistuba, V. Schurig, *LC-GC Eur.* **2009**, *22*, 60-69; c) S. K. Weber, S. Bremer, O. Trapp, *Chem. Eng. Sci.* **2010**, *65*, 2410-2416.

Received: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

A series of hydroquinidine derivatives embedded into elastomeric silicone films were prepared and used as insoluble organocatalysts in the asymmetric dimerization of ketenes. A protocol was also introduced for comparing the productivity/enantioselectivity performances of the supported catalyst with those of the analogous soluble counterparts.



Damiano Cancogni, Alessandro Mandoli,* Ravindra P. Jumde, and Dario Pini. Page No. – Page No.

Silicone-supported Cinchona alkaloid derivatives as insoluble organocatalysts in the enantioselective dimerization of ketenes.

Keywords: Asymmetric Catalysis / Cinchona Alkaloids / Ketene Dimerization / Organocatalysis / Silicones / Supported Catalysts