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Supported Catalysts

New Polymer-Supported Mono- and Bis-*Cinchona* Alkaloid Derivatives: Synthesis and Use in Asymmetric Organocatalyzed Reactions

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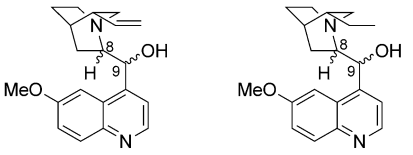
Abstract: The straightforward synthesis of polystyrene-supported *Chinchona* alkaloids and their application in the asymmetric dimerization of ketenes is reported. Six different immobilized derivatives, consisting of three dimeric and two monomeric 9-*O* ethers, were prepared by "click" anchoring of soluble alkaloid precursors on to azidomethyl resins. The resulting insoluble polymer-bound (IPB) organocatalysts were employed for promoting the dimerization of in-situ generated ketenes. After opening of the ketene dimer intermediates with *N*,*O*-dimethylhydroxylamine, valuable Weinreb amides were eventually obtained in good yield (up to 81%) and excellent enantiomeric purity (up to 96% *ee*). All of the IPB catalysts could be recycled effectively without significant loss of activity and enantioselectivity. The extension to other asymmetric transformations (*meso*-anhydride desymmetrization and α-amination of 2-oxindoles) is also briefly discussed.

Introduction

The covalent immobilization of *Cinchona* alkaloids **1**–**4** (Figure 1) onto insoluble supports has been reported several times over the last four decades.[1] By exploring different materials and alternative anchoring strategies, a large number of insoluble polymer-bound (IPB) derivatives have been disclosed, which afforded excellent activity and enantioselectivity in both metal-catalyzed[2] and organocatalyzed asymmetric transformations.[3,4] Nonetheless, this specific topic may be taken as paradigmatic of the whole field of supported asymmetric catalysts, in that the easy recovery and reuse of the expensive chiral auxiliary was seemingly not sufficient for triggering the use of IPB systems in the large-scale production of fine-chemicals.[1f]



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

Figure 1. *Cinchona* alkaloids: structures, acronyms, and numbering scheme.

One of the reasons of this limited popularity is undoubtedly the complex synthesis and the associated high costs of many of the IPB systems reported so far. In fact, very few examples are known in which the preparation of the supported *Cinchona* alkaloid derivative appears straightforward enough to be reasonably fit for subsequent scale-up. Mostly, these examples consist of quaternary ammonium salts or simple esters covalently anchored to organic or inorganic materials through the quinuclidine nitrogen or the 9-OH group of the native alkaloid (e.g., **P5** and **P6** in Figure 2).[4] On the contrary, the preparation of IPB 9-*O* ethers, including the effective bis-alkaloid ones with an aromatic central spacer (e.g., **P7** and **P8**), turned out to be far less convenient. In these cases major drawbacks arose from the complex synthesis of a soluble precursor suitable for anchoring or the occurrence of extensive leaching when the IPB system was employed as a catalyst precursor.[2a]

In order to overcome these limitations, we recently introduced a simple and scalable protocol for the preparation of IPB quinidine ethers of the pyridazine class (**P9**).[5] The key element of such an approach was the choice of the Cu-catalyzed azide–alkyne cycloaddition (CuAAC) as the tool for linking alkyne-functionalyzed alkaloid derivatives to insoluble azidomethylpolystyrene supports.[6] Gratifyingly, this "click-chemistry" strategy allowed a significant overall improvement of the preparation of IPB materials, including the straightforward and chromatography-free synthesis of anchorable chiral derivatives and the attainment of unprecedentedly high anchoring yields and alkaloid loadings in the immobilization step.

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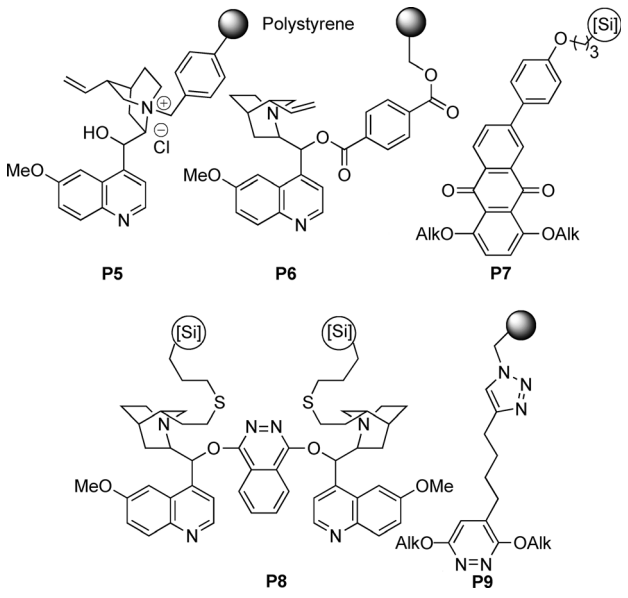


Figure 2. Typical IPB-*Cinchona* alkaloid derivatives (Alk = QD or DHQD).

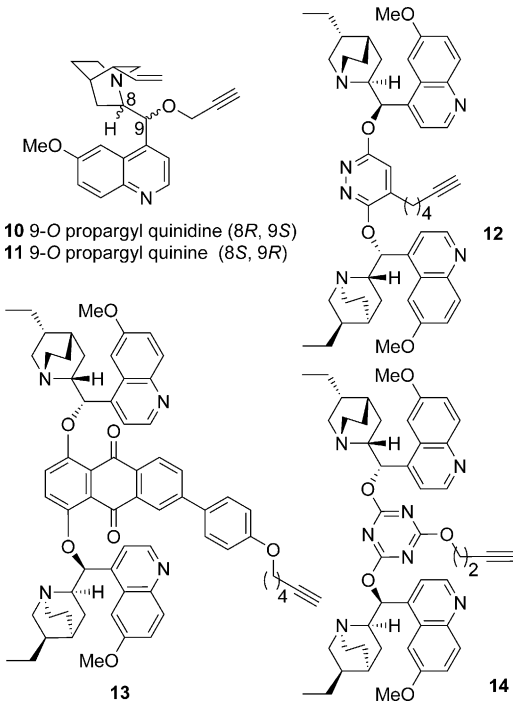


Figure 3. Clickable-alkaloid derivatives used in this work.

With the aim of documenting the scope of the "click" route to IPB *Cinchona* alkaloids, we report herein the preparation of six new 9-*O* ether derivatives bound to gel-type polystyrene resins.

In addition to describing the synthesis of suitable soluble precursors and their immobilization, the screening of the resulting materials as insoluble organocatalysts in a benchmark asymmetric dimerization reaction of ketenes[7] is discussed and compared with that of **P9**. The use of the supported alkaloids in other asymmetric transformations is also briefly examined.

Results and Discussion

Synthesis of soluble alkyne-*Cinchona* derivatives

The structures of the anchorable precursors selected in the present study (Figure 3) encompass mono- (**10** and **11**) and bis-alkaloid ethers (**12**–**14**). As anticipated, all of the soluble derivatives were provided with a terminal alkyne group in order to allow their "click" immobilization onto azidomethyl-substituted resins.

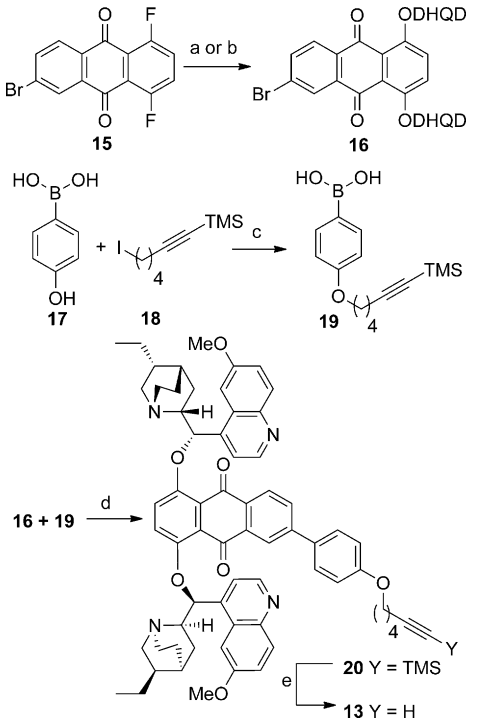
The choice of **10** and **11** was prompted by the lack of literature precedents about the use of ligands and organocatalysts with a 1*H*-1,2,3-triazol-4-ylmethyl substituent at the alkaloid 9-*O* position. Moreover, the possibility of obtaining **10** and **11** in one step from commercial chemicals, as well as the reported feasibility of their synthesis in multi-kilogram amounts,[8] made the compounds appealing for the access to potentially scalable IPB systems.

Concerning the bis-alkaloid organocatalysts, the pyridazine ether of 10,11-dihydroquinine (**12**) was included for the sake of comparison with early results provided by its pseudoenantiomeric counterparts of the quinidine series.[5] The preparation of **12** followed the synthetic pathway already adopted for the latter:[5] The central heterocyclic spacer with a terminal alkyne moiety was obtained first by an inverse electron demand Diels–Alder/N_2 extrusion reaction between 1,4-dichlorotetrazine and an excess of 1,7-octadiyne. Next, the resulting substituted 1,4-dichloropyridazine was reacted with two equivalents of **4** in toluene, in the presence of KOH, to give **12**. As in the previous study, also in this case the crude product could be isolated in sufficiently pure form after solvent extraction, to be used without further treatment in the subsequent immobilization step (see the Supporting Information).

After their introduction as ligands in the osmium-catalyzed asymmetric dihydroxylation and aminohydroxylation,[9] bis-alkaloid ethers with a central anthraquinone core have been extensively explored in various metal-free asymmetric transformations.[10] Molecularly enlarged and IPB variants of this class were also described, with linear polystyrene, PEG, and silica gel (e.g., **P7**) being employed as the support material.[11]

However, to the best of our knowledge, no example of immobilization onto cross-linked polystyrene has been reported to date. Having in mind the versatility and the unique properties of these chiral auxiliaries, **13** was designed as a competent anchorable derivative.

Apart from the introduction of the terminal alkyne unit required by the "click" approach, the synthesis of **13** (Scheme 1) was largely modelled onto that described by Bolm and coworkers for their silica-gel supported ligand.[11a,b] The halogenated anthraquinone **15** was prepared in two steps from 1,4-difluorobenzene and 4-bromophthalic anhydride,[12] and then reacted with the deprotonated alkaloid to afford the bis-ether **16**. Initial attempts to carry out the latter transformation as described, with the lithium salt of **3** in THF,[11a,b] were just partially successful because ^{1}H NMR and TLC monitoring of the reaction



Scheme 1. (a) **3** (2.5 equiv), *n*BuLi (2.5 equiv), THF, rt, 18 h then 40 °C, 18 h; (b) **3** (2.05 equiv), NaH (2.1 equiv), DMF, rt, 18 h.; (c) K_2CO_3, acetone or DMF, rt → 65 °C; (d) $Pd(PPh_3)_4$ (8.6 mol%), Na_2CO_3 (4.6 equiv), toluene/EtOH/H_2O (10:1:1), reflux 4 h → rt, overnight; (e) K_2CO_3 (1.2 equiv), MeOH/CH_2Cl_2 (5:1), rt, 64 h.

progress showed an incomplete conversion even after 36 h. This resulted in a crude mixture containing at least three main alkaloid derivatives (**16**, the corresponding mono-substituted intermediates, and unreacted **3**), whose chromatographic separation afforded **16** in only moderate yield (39%). After some experimentation, better results were obtained by the use of the sodium salt of **3** in DMF. Under these conditions, the conversion of **15** was complete in 18 h, and crude **16** obtained after extractive workup was shown by ^{1}H NMR spectroscopy to contain excess **3** and residual DMF as the only significant contaminants.

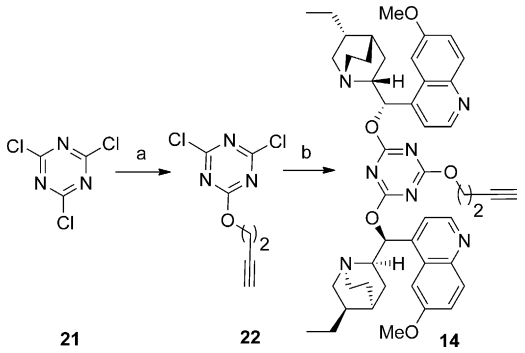
Therefore, the unpurified material (approx. 87 wt% of **16**, 95% yield) was employed directly in the subsequent Suzuki–Miyaura cross-coupling with the boronic acid derivative **19**. The latter was prepared by the reaction of commercial **17** with the protected iodoalkyne **18**[13] in the presence of potassium carbonate. In DMF the reaction proceeded uneventfully to complete conversion to afford a crude product showing a single spot by TLC. After extractive workup and drying, **19** was obtained in good yield (83%) and in sufficiently pure form (approx. 95 wt% by ^{1}H NMR) to be used directly in the next step.

The cross-coupling between **16** and **19**, under conditions similar to those described,[11a,b] proceeded smoothly to completion in 18 h. Extractive workup of the mixture led to the removal of the excess of boronic acid and other neutral by-products, affording **20** in good yield (72%) and purity (single TLC spot). This conclusion was confirmed by comparing the ^{1}H NMR spectrum of crude **20** with that of a sample purified chromatographically (see the Supporting Information).

The deprotection of **20** with K_2CO_3 in MeOH/CH_2Cl_2[14] afforded **13** in essentially quantitative yield. Also in this case, examination of the ^{1}H NMR spectrum of the product obtained after removal of the volatiles revealed that the crude product was free from major contaminants. This result prompted its use in the "click" anchoring step without further purification.

The commercial availability of phthalazine, anthraquinone, and diphenylpyrimidine dimeric 9-*O* ethers of *Cinchona* alkaloids is undoubtedly boosting their popularity as organocatalysts. However, given the strong influence often exerted by the central aromatic spacer on catalytic performance, it cannot be excluded that better catalysts could be eventually discovered by tuning the structure of the linking group. In this respect, examination of the literature revealed that compounds with a strongly electron-poor central spacer, like the 1,3,5-triazine one, have been largely overlooked. To the best of our knowledge, only two examples have been reported to date for the use of derivatives of this sort in either metal-catalyzed[15] or organocatalyzed reactions.[16] Considering also that the stepwise nucleophilic substitution of the halogen atoms of cyanuric chloride (**21**) can easily provide non-symmetrical derivatives suitable for anchoring to insoluble supports,[17] the development of the new organocatalyst **14** was decided.

The first step of the synthesis of **14** (Scheme 2) required the



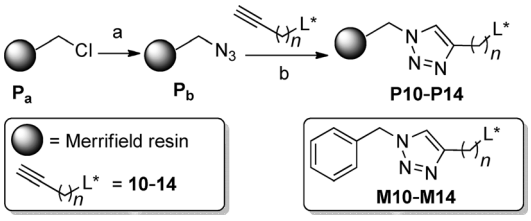
Scheme 2. (a) 3-Butyn-1-ol (0.78 equiv), DIPEA (1.41 equiv), THF, rt, 18 h; (b) **3** (2 equiv), NaH (2 equiv), THF, rt, 18 h.

preparation of the dichlorotriazine **22**, which was obtained by modification of the literature procedure for the corresponding propargyl lower homologue.[18] Accordingly, **21** was reacted with 3-butyn-1-ol and an excess of *N*,*N*-diisopropylethylamine (DIPEA) to give **22** in good yield (73%) after chromatographic purification. Next, the double nucleophilic displacement of the residual chlorine atoms of **22** was carried out with deprotonated hydroquinidine. With this aim, the alkaloid **3** was converted into the corresponding sodium alkoxide by treatment with NaH in THF, and the resulting solution was added to **22** and stirred at room temperature for 18 h. The ^{1}H NMR spectrum of the crude product showed a good conversion, with the presence of only 5–10% of two alkaloid species other than the product (unreacted **3** and the mono-substituted alkaloid inter-

mediate en route to **14**). For characterization purposes the crude product was subjected to purification by flash chromatography to give an analytically pure fraction (39% yield), whose spectroscopic features were in accordance with the structure of **14** (see the Supporting Information). Even though the isolated yield was not high in this case, it should be pointed out that this was largely due to the need of discarding several chromatographic fractions showing minor spots by TLC. Given the nature of the contaminants and their low concentration in the crude product, it is not excluded, therefore, that a more effective procedure could involve the direct "click" immobilization of unpurified **14** (as for **12** and **13**, see below).

"Click" immobilization of alkyne-*Cinchona* derivatives onto azido-Merrifield resin and preparation of soluble models

Having established convenient routes to the alkaloid derivatives provided with a terminal alkyne moiety, the next goal was their immobilization onto an azido-functionalized insoluble polymer. For this purpose, the gel-type azidomethylpolystyrene material $\mathbf{P_b}$ was selected as the support. It was prepared from the commercial Merrifield resin $\mathbf{P_a}$ (2.3 mmol Cl g^{-1}) by heating with an excess of sodium azide in dry DMSO (Scheme 3).[19] The reaction was carried out under slow stirring



Scheme 3. (a) NaN_3, DMSO, 60 °C, 3 d; (b) CuI (5 mol%), DIPEA (1 equiv), CH_2Cl_2, rt, 2 d (for the structures of **10–14**, see Figure 3).

for three days in order to avoid mechanical damage of the polymer beads. After filtration of the suspension, thorough washing, and drying under reduced pressure, $\mathbf{P_b}$ was obtained as an off-white solid in 95% recovery yield. The introduction of N_3 groups was confirmed by the observation of the strong azide IR stretching (2095 cm^{-1})[20] and by the positive Kaiser test with PPh_3/ninhydrin.[21] According to nitrogen elemental analysis (9.3 wt%, 2.2 mmol N_3 g^{-1}) and negative 4-nitrobenzylpyridine color test,[22] no significant amounts of residual chlorine from the starting Merrifield resin $\mathbf{P_a}$ remained in the azidomethyl material $\mathbf{P_b}$.

The immobilization of **10–14** onto the polystyrene support was achieved by the anticipated "click" reaction between the alkyne-functionalized alkaloids (**12** and **13** in the crude form) and $\mathbf{P_b}$ in the presence of the CuI-DIPEA catalytic system (Scheme 3). After two days of gentle shaking, the functionalized resins were filtered and washed exhaustively for removing the copper salt and any free alkaloid species. Drying to constant weight under vacuum afforded the insoluble materials **P10–P14**, which were characterized by IR spectroscopy (see the Supporting Information).

Due to the large nitrogen content of the polymer support, the alkaloid loading was not determined by elemental analysis. Instead, it was estimated by the weight increase over the starting azidomethyl resin $\mathbf{P_b}$ (Table 1).[23] This evidence confirmed

Table 1. Results in the "click" immobilization of **10–14**.

Entry	Soluble alkaloid derivative	Resin	Organocatalyst loading [mmol g^{-1}][c]
1	**10**	**P10**	0.77
2	**11**	**P11**	0.69
3	**12**	**P12**	0.25
4	**13**	**P13**	0.18
5	**14**	**P14**	0.20

[a] Alkaloid content in **P10–P14**, calculated from the weight increase.

the successful immobilization of the chiral units onto $\mathbf{P_b}$, although to an extent that proved larger for the propargyl mono-ethers **10** and **11** (Table 1, entries 1 and 2) than for the bis-alkaloid derivatives **12–14** (Table 1, entries 3–5). Even though no explanation can be provided at the moment for this trend, according to our experience, this can be due in part to the relatively small scale of the preparations carried out in the present study.[24]

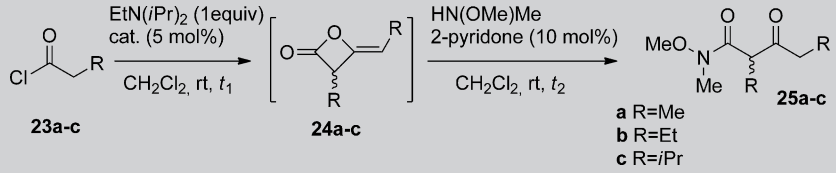
In order to carry out a proper comparison with the homogeneous phase, the soluble model compounds **M10–M14** (Scheme 3) were synthesized by "click" addition of benzylazide to **10–14**. The fair to good yields obtained in these preparations (see the Supporting Information) provide validation of the chemistry involved in the anchoring step.

Homogeneous and heterogeneous asymmetric dimerization of ketenes

To test the organocatalytic properties of the newly prepared IPB *Cinchona* alkaloid derivatives in the asymmetric dimerization of ketenes (Table 2), **P10–P14** were employed under the conditions described by Calter and co-workers for the in situ generation of ketenes from acid chlorides.[7] As in the previous studies,[5,25] the overall transformation which leads from the starting material (**23a–c**) to the final Weinreb amide (**25a–c**) was not carried out one-pot. Instead, after the time t_1 for acid chloride dehydrochlorination and ketene dimerization, the solution containing the β-lactone intermediate (**24a–c**) was separated from the IPB organocatalyst by filtration under an inert atmosphere. The filtrate was then treated in a separate vessel with *N,O*-dimethylhydroxylamine and a catalytic amount of 2-pyridone (time t_2) to achieve the ring opening of **24a–c** to the final product **25a–c**. The latter was isolated by careful aqueous work-up and, thanks to the lack of any organocatalyst contaminant, it generally displayed a high chemical purity after removal of the volatiles. The results of these runs (Table 2) revealed that all of the chiral IPB derivatives behaved as heterogeneous enantioselective catalysts in the transformation under study.[26]

When the supported mono-quinidine ether **P10** was employed in the reaction of propanoyl chloride (**23a**), the syn-

Table 2. Results in the asymmetric dimerization of ketenes with IPB and soluble *Cinchona* alkaloid derivatives.



Entry	Catalyst	Cycle	Acid chloride	t_1 [h]	t_2 [h]	Product	Yield [%][a]	*Ee* [%][b,c]	Configuration[d]
1	**P10**	1	**23a**	6	2	**25a**	70	91 (93)	*S*
2	**P10**	2	**23b**	6	2	**25b**	63	95 (95)	*S*
3	**P10**	3	**23c**	24	24	**25c**	61	93 (95)	*S*
4	**P11**	1	**23a**	6	2	**25a**	65	70 (70)	*R*
5	**P11**	2	**23b**	6	2	**25b**	68	68 (70)	*R*
6	**P11**	3	**23c**	24	24	**25c**	63	62 (69)	*R*
7[e,f]	**P9** (Alk = DHQD)	1	**23a**	6	2	**25a**	60	97 (95)	*S*
8[e,f]	**P9** (Alk = QD)	2	**23b**	6	2	**25b**	56	97	*S*
9[e,f]	**P9** (Alk = QD)	3	**23c**	24	24	**25c**	61	97	*S*
10	**P12**	1	**23a**	6	2	**25a**	75	61 (77)	*R*
11	**P12**	2	**23b**	6	2	**25b**	81	82 (88)	*R*
12	**P12**	3	**23c**	24	24	**25c**	42	89 (92)	*R*
13[f]	**P13**	1	**23a**	6	2	**25a**	58	87 (89)	*S*
14[f]	**P13**	2	**23b**	6	2	**25b**	63	92 (92)	*S*
15[f]	**P13**	3	**23c**	24	24	**25c**	53	93 (93)	*S*
16	**P14**	1	**23a**	6	2	**25a**	78	90 (92)	*S*
17	**P14**	2	**23b**	6	2	**25b**	80	93 (93)	*S*
18	**P14**	3	**23c**	24	24	**25c**	69	96 (96)	*S*

[a] Isolated yields. [b] In parentheses, data with soluble model catalysts **M10**–**M14**. [c] Determined by HPLC on chiral stationary phases (see the Supporting Information). [d] Configuration of the major enantiomer by the HPLC elution order. [e] Data taken from ref. [5]. [f] 2.5 mol% of catalyst was used.

thetically valuable amide (*S*)-**25a**[27] was isolated in good yield and excellent enantiopurity (Table 2, entry 1). After rinsing with dry solvent, the recovered IPB catalysts showed a similarly high activity and stereoselectivity in the dimerization of the ketenes obtained from the homologous acid chlorides **23b** and **23c** (Table 2, entries 2 and 3).

As expected,[7] switching to the IPB catalyst **P11** (quinine series) caused the prevalent formation of (*R*)-configured products **25a**–**c** (Table 2, entries 4–6), albeit with a reduced enantiomeric purity. Comparison with the results provided by the soluble model **M11** in the homogeneous phase (data in parentheses in Table 2) demonstrates that this result was not a heterogenization-related issue. On the contrary, the enantioselectivity drop appears to be largely caused by the diastereomeric relationship between the alkaloids belonging to either the quinidine or quinine series, respectively.[28] A similar effect is observed by contrasting the *ee* values provided by **P12** (Table 2, entries 10–12) with that of the pseudoenantiomeric organocatalyst **P9** (Alk = QD or DHQD) examined in our previous investigation (for the sake of comparison, the results with **P9** are reported in Table 2, entries 7–9).[5] It is interesting to note that these findings mirror to a large extent those of Calter and coworkers, with **P11** and **P12** (and the corresponding soluble models **M11** and **M12**) behaving like quinine derivatives with small to medium-sized 9-*O* substituents (e.g. 9-*O*-propanoyl- and 9-*O*-benzoylquinine, which afford **25a** with 69% *ee* and 80% *ee*, respectively).[7,27b,c]

Examination of the novel bis-ethers **P13** (Table 2, entries 13–15) and **P14** (Table 2, entries 16–18) led to *ee* values in the range observed for the other organocatalysts of the quinidine series. With both alkaloid derivatives the enantiomeric purity of the product improved slightly on increasing the steric requirements of the R group in the starting acid chloride.[29] Eventually, this positive trend allowed us to attain enantioselectivity levels that approach the best results reported to date in the asymmetric dimerization of ketenes with either soluble[7,27] or insoluble alkaloid derivatives.[5,25]

Closer examination of the data in Table 2 prompts some additional comment. First of all, in most of the runs the yield and *ee* values obtained by the use of IPB alkaloid derivatives **P10**–**P14** match within a few percent with those afforded by the corresponding soluble models **M10**–**M14**. Therefore, the combination of a gel-type polystyrene support with CuAAC is confirmed as an effective and general tool for transferring the high chemical and stereochemical efficiency of a *Cinchona* alkaloid organocatalyst from the homogeneous to the heterogeneous phase. From this point of view the approach described herein seems to avoid much of the problems encountered with alternative immobilization schemes, most notably concerning the leftover of interfering functional groups at the surface of the heterogenized alkaloid organocatalyst.[30]

Moreover, in spite of the molecular diversity encompassed by the organocatalysts of the present as well as previous studies,[5,7,25,27] the outcome of the catalyzed reaction proved rather uniform. This is particularly evident for the most effective derivatives of the quinidine series, where the seemingly large variations in the structure of the 9-*O* substituent turned out to have a minor impact on the enantiomeric purity of the prod-

ucts **25a–c** (*ee* values mostly falling in the 92–96% range). At variance with other enantioselective transformations mediated by *Cinchona* alkaloid derivatives,[31] and according to the chiral induction model originally depicted by Calter,[32] it seems then unlikely that either the electronic or the steric properties of the 9-*O* substituent may play a specific role in the chiral induction mechanism. On the contrary, these findings suggest a reactive conformation where the catalytic site (quinuclidine nitrogen)[7,32] and the derivatizing group are far apart each other, like in the working model for *meso* anhydride desymmetrization proposed by Deng and co-workers.[33]

Finally, even though a detailed recycling study was not carried out in the present investigation, it is worth noting that all of the IPB organocatalysts were recovered and used at least three times with fair to excellent results and no sign of cross contamination in the sequential screening of different substrates.

Screening in other organocatalyzed enantioselective transformations

To further explore the scope of the materials obtained by the "click" route, two additional processes were chosen (Scheme 4). In these transformations, the alkaloid derivatives are believed to act as a chiral base catalysts,[31,33,34] instead of nucleophilic catalysts as in the ketene dimerization reaction examined above.[7,32]

Based on literature precedents in the homogeneous phase,[35] the desymmetrization of tetrahydrophthalic anhydride (**26**) was tackled by examining alkaloid organocatalysts with an anthraquinone core. Not unexpectedly, the use of **P13** proved largely unsatisfactory in this process, possibly due to the collapse of the polystyrene backbone in the reaction medium containing a relatively large amount (2%) of methanol. For this reason the immobilization of the anthraquinone derivative onto a more hydrophilic support was performed. Eventually, this led to the preparation of material **P15**, obtained by "click" anchoring of **13** to an azidomethyl resin embedding oligo(ethylene oxide) polar grafts and cross-linking units (see the Supporting Information).[2a,36] With this modification the activity of the supported organocatalyst increased appreciably, allowing the isolation of the hemiester **27** in fair yields and reasonable enantiomeric purity when the reaction was carried out in THF or toluene at −20 °C.

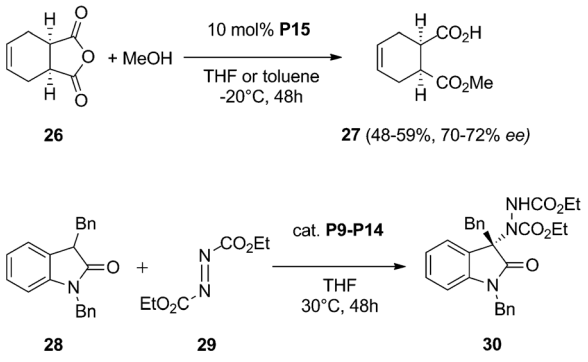
These results are slightly better than those described for native quinidine and for quinine anthraquinone ether anchored onto siliceous supports through the C9—C10 position.[3a,b] By contrast, the enantioselectivity afforded by **P15** appears lower than reported for the corresponding quinine anthraquinone ether on silica gel (92% *ee* in the methanolysis of **26**).[3c]

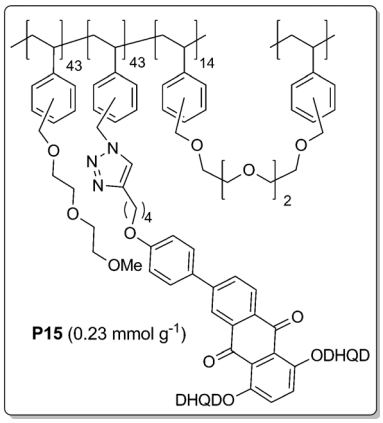
The heterogeneous asymmetric α-amination of the 2-oxindole **28** with diethyl azodicarboxylate (**29**) was explored under conditions similar to those employed by Barbas III in the homogeneous phase.[34] Thanks to the use of an aprotic reaction medium, switching to a more hydrophilic support was not necessary in this case. On the contrary, all of the alkaloid derivatives anchored onto the standard Merrifield resin [**P9** (Alk = QD) and **P10**–**P14**] smoothly afforded the product **30** in good to nearly quantitative yield (Table 3). At variance with the dimerization of ketenes discussed above, in this case the enantiomeric purity of the aminated oxindole proved strongly dependent on the structure of the alkaloid derivative. Best results (84–92% *ee*) were obtained with the supported pyridazine ethers **P9** (Alk = QD) and **P12** that, in fact, bear the closest structural similarity with the optimal soluble organocatalyst disclosed by Barbas III (10 mol% of DHQD phthalazine ether, 99% *ee* in Et_2O as the solvent).[34]

Table 3. Results in the α-amination of **28** with **29**.

Entry	Catalyst [mol%]	Product **30** Yield [%][a]	*Ee* [%][b]	Configuration[c]
1	**P9** (Alk = QD, 10)	**72**	92	(*S*)
2	**P10** (20)	>**95**	46	(*S*)
3	**P11** (20)	>**95**	20	(*R*)
4	**P12** (10)	>**95**	84	(*R*)
5	**P13** (10)	>**95**	28	(*S*)
6	**P14** (10)	>**95**	66	(*S*)

[a] Isolated yield after column chromatography. [b] Determined by HPLC on chiral stationary phases (see the Supporting Information). [c] Configuration of the major enantiomer by the HPLC elution order (ref. [34]).





Scheme 4. Additional asymmetric transformations catalyzed by supported alkaloid derivatives.

Conclusions

A series of six new IPB organocatalysts **P10**-**P15** have been prepared by a "click-chemistry" approach relying on the copper-catalyzed anchoring to azidomethyl resins of *Cinchona* alkaloid 9-*O* ethers provided with a terminal alkyne group.

Thanks to previous results from the literature as well as the design of new derivatives and the optimization work disclosed herein, four out of the five an-

chorable organocatalysts included in this study could be prepared by chromatography-free, high-yielding, concise synthetic routes.

The covalent immobilization of the chiral derivatives onto the resin support was achieved by a very simple and affordable "click" procedure. Even though additional work will be required for optimizing the anchoring in some cases, it is worth noting that for the 9-*O* propargyl ether **10** nearly complete capture by the polystyrene resin was attained. Taken together with our previous results for **P9**, these findings suggest that the "click-chemistry" approach is a general and potentially highly effective option for the multigram-scale preparation of mono- and bis-9-*O* alkaloid ethers immobilized onto an insoluble support.

Benchmarking of the new IPB organocatalysts in the heterogeneous asymmetric dimerization of ketenes provided fair to good yields (42–81%) and *ee* values (61–96%). These results are comparable to those observed by using competent model compounds, as well as soluble alkaloid derivatives from the literature. To confirm that the architecture of IPB alkaloid ethers obtained by the CuAAC "click-chemistry" route is well suitable for organocatalytic applications, their use was briefly examined in two additional asymmetric processes: The desymmetrization of a *meso*-anhydride and the α-amination of a 2-oxindole.

In conclusion, the work discussed herein demonstrates the possibility of developing IPB *Cinchona* alkaloid organocatalysts that combine a straightforward and scalable preparation with the attainment of excellent organocatalytic properties.

A comprehensive investigation of the new materials in asymmetric transformations other than ketene dimerization is currently underway and will be reported in due course.

Experimental Section

For the general methods, materials, analytical procedures, and characterization data of all new compounds, see the Supporting Information.

Preparation of P10–P14 by "Click" Anchoring 10–14 onto Azido-Merrifield Resin

General procedure: A 25 mL Schlenk tube was charged with the azido-Merrifield resin $\mathbf{P_b}$ (0.500 g, 2 equiv N_3 groups). After degassing for 10 min at 5 mm Hg, freshly distilled CH_2Cl_2 (5 mL) was added under nitrogen, followed by a solution/suspension of the alkaloid derivative **10**–**14** (0.55 mmol, 1 equiv), CuI (5 mol%), and DIPEA (1 equiv) in CH_2Cl_2 (5 mL). The Schlenk tube was sealed under nitrogen and kept on an orbital shaking platform for 2–3 days at room temperature. The mixture was filtered under air through a glass frit and washed several times with portions of CH_2Cl_2, aqueous ammonia/THF, methanol, THF, and CH_2Cl_2. After drying to constant weight under vacuum (0.05 mm Hg), the recovered resin was characterized by IR spectroscopy (see the Supporting Information). The alkaloid loading was determined by the mass difference between the recovered material (**P10**–**P14**) and the starting azido-methyl resin ($\mathbf{P_b}$, see Table 1).

Heterogeneous Asymmetric Dimerization of Ketenes

General Procedure: A 25 mL Schlenk tube fitted with a medium porosity glass frit and stopcock side arm was charged under nitrogen with the supported organocatalyst (**P10**–**P14**, 0.05 mmol of alkaloid derivative, 5 mol%) and dry CH_2Cl_2 (10 mL). After stirring for 10 min, DIPEA (170 μL, 1.0 mmol) and freshly distilled acid chloride (**23a**–**c**, 1.0 mmol) were added. The flask was closed under nitrogen and kept stirring slowly at room temperature, for the time t_1 (Table 2). The mixture was then filtered through the enclosed frit into a dry Schlenk tube and the IPB-catalyst was rinsed with CH_2Cl_2 (2×2.5 mL). The combined filtrates were treated under nitrogen with HN(OMe)Me (37 μL, 0.50 mmol) and 2-hydroxypyridine (4.7 mg, 0.05 mmol) and the resulting solution was stirred at room temperature for the time t_2 (Table 2). For *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 (for the conditions, see Ref. [5]). The remaining part of the solution was worked-up as described,[5] purifying the product **25a**–**c** by filtration through silica gel. After brief drying under vacuum, the frit-retained polymeric catalyst was returned into the flask and directly used in further catalysis cycles.

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Keywords: asymmetric catalysis · *Cinchona* alkaloids · click chemistry · desymmetrization · ketenes · supported catalysts

[1] a) V. D. E. De, I. F. J. Vankelecom, P. A. Jacobs, Editors *Chiral Catalyst Immobilization and Recycling*, Wiley-VCH, Weinheim, **2000**; b) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401–3429; c) M. Benaglia, *New J. Chem.* **2006**, *30*, 1525–1533; d) A. F. Trindade, P. M. P. Gois, C. A. M. Afonso, *Chem. Rev.* **2009**, *109*, 418–514; e) J. Lu, P. H. Toy, *Chem. Rev.* **2009**, *109*, 815–838; f) T. E. Kristensen, T. Hansen, *Eur. J. Org. Chem.* **2010**, 3179–3204; g) T. Marcelli, H. Hiemstra, *Synthesis* **2010**, 1229–1279; h) T. Tsubogo, T. Ishiwata, S. Kobayashi, *Angew. Chem. Int. Ed.* **2013**, *52*, 6590–6604; *Angew. Chem.* **2013**, *125*, 6722–6737; i) A. Puglisi, M. Benaglia, V. Chiroli, *Green Chem.* **2013**, *15*, 1790–1813.

[2] a) A. Mandoli, D. Pini, M. Fiori, P. Salvadori, *Eur. J. Org. Chem.* **2005**, 1271–1282; b) J. Achkar, J. R. Hunt, R. L. Beingessner, H. Fenniri, *Tetrahedron: Asymmetry* **2008**, *19*, 1049–1051; c) R.-t. Cha, S.-y. Wang, S.-l. Cheng, *J. Appl. Polym. Sci.* **2008**, *108*, 845–849; d) D. Lee, J. Lee, H. Lee, S. Jin, T. Hyeon, B. M. Kim, *Adv. Synth. Catal.* **2006**, *348*, 41–46; e) M. S. Sarkar, J.-Y. Jung, M.-J. Jin, *Stud. Surf. Sci. Catal.* **2007**, *165*, 705–708.

[3] a) F. Bigi, S. Carloni, R. Maggi, A. Mazzacani, G. Sartori, G. Tanzi, *J. Mol. Catal. A* **2002**, *182–183*, 533–539; b) Y.-M. Song, J. S. Choi, J. W. Yang, H. Han, *Tetrahedron Lett.* **2004**, *45*, 3301–3304; c) H. S. Kim, Y.-M. Song, J. S. Choi, J. W. Yang, H. Han, *Tetrahedron* **2004**, *60*, 12051–12057; d) P. Yu, J. He, L. Yang, M. Pu, X. Guo, *J. Catal.* **2008**, *260*, 81–85; e) S. H. Youk, S. H. Oh, H. S. Rho, J. E. Lee, J. W. Lee, C. E. Song, *Chem. Commun.* **2009**, 2220–2222; f) Q. Chen, C. Xin, L.-L. Lou, K. Yu, F. Ding, S. Liu, *Catal. Lett.* **2011**, *141*, 1378–1383; g) J. Zhou, J. Wan, X. Ma, W. Wang, *Org. Biomol. Chem.* **2012**, *10*, 4179–4185.

[4] a) A. M. Hafez, A. E. Taggi, H. Wack, W. J. Drury III, T. Lectka, *Org. Lett.* **2000**, *2*, 3963–3965; b) R. Chinchilla, P. Mazon, C. Najera, *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281; c) B. Thierry, J.-C. Plaquevent, D. Cahard, *Tetrahedron: Asymmetry* **2001**, *12*, 983–986; d) A. M. Hafez, A. E. Taggi, T. Dudding, T. Lectka, *J. Am. Chem. Soc.* **2001**, *123*, 10853–10859;

e) B. Thierry, T. Perrard, C. Audouard, J.-C. Plaquevent, D. Cahard, *Synthesis* **2001**, 1742 – 1746; f) A. M. Hafez, A. E. Taggi, T. Lectka, *Chem. Eur. J.* **2002**, *8*, 4114 – 4119; g) R. Chinchilla, P. Mazon, C. Najera, *Adv. Synth. Catal.* **2004**, *346*, 1186 – 1194; h) R. Chinchilla, P. Mazon, C. Najera, *Molecules* **2004**, *9*, 349 – 364; i) B. Thierry, J.-C. Plaquevent, D. Cahard, *Mol. Diversity* **2005**, *9*, 277 – 290; j) S. France, D. Bernstein, A. Weatherwax, T. Lectka, *Org. Lett.* **2005**, *7*, 3009 – 3012; k) Q. Shi, Y.-J. Lee, H. Song, M. Cheng, S.-s. Jew, H.-g. Park, B.-S. Jeong, *Chem. Lett.* **2008**, *37*, 436 – 437; l) R. Chinchilla, C. Najera, F. J. Ortega, S. Tari, *Tetrahedron: Asymmetry* **2009**, *20*, 2279 – 2286; m) S.-s. Jew, H.-g. Park, *Chem. Commun.* **2009**, 7090 – 7103; n) Y. Qin, G. Yang, L. Yang, J. Li, Y. Cui, *Catal. Lett.* **2011**, *141*, 481 – 488; o) L. Yang, D. Zhou, C. Qu, Y. Cui, *Catal. Lett.* **2012**, *142*, 1405 – 1410; p) P. Ahamed, M. A. Haque, M. Ishimoto, M. M. Parvez, N. Haraguchi, S. Itsuno, *Tetrahedron* **2013**, *69*, 3978 – 3983.

[5] R. P. Jumde, A. Mandoli, F. De Lorenzi, D. Pini, P. Salvadori, *Adv. Synth. Catal.* **2010**, *352*, 1434 – 1440.

[6] A. E. Fernandes, A. M. Jonas, O. Riant, *Tetrahedron* **2014**, *70*, 1709 – 1731.

[7] M. A. Calter, R. K. Orr, W. Song, *Org. Lett.* **2003**, *5*, 4745 – 4748.

[8] Y. Ishii, R. Fujimoto, M. Mikami, S. Murakami, Y. Miki, Y. Furukawa, *Org. Process Res. Dev.* **2007**, *11*, 609 – 615.

[9] H. Becker, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448 – 451; *Angew. Chem.* **1996**, *108*, 447 – 449.

[10] a) L. Tang, L. Deng, *J. Am. Chem. Soc.* **2002**, *124*, 2870 – 2871; b) H.-L. Cui, J. Peng, X. Feng, W. Du, K. Jiang, Y.-C. Chen, *Chem. Eur. J.* **2009**, *15*, 1574 – 1577; c) W. Yang, X. Wei, Y. Pan, R. Lee, B. Zhu, H. Liu, L. Yan, K.-W. Huang, Z. Jiang, C.-H. Tan, *Chem. Eur. J.* **2011**, *17*, 8066 – 8070; d) B. Zhu, L. Yan, Y. Pan, R. Lee, H. Liu, Z. Han, K.-W. Huang, C.-H. Tan, Z. Jiang, *J. Org. Chem.* **2011**, *76*, 6894 – 6900.

[11] a) C. Bolm, A. Maischak, *Synlett* **2001**, 93 – 95; b) J. Wöltinger, H.-P. Krimmer, K. Drauz, *Tetrahedron Lett.* **2002**, *43*, 8531 – 8533; c) J. Wöltinger, H. Henniges, C. Bolm, A. Maischak, O. Burkhardt, D. Reichert, A. Karau, J.-L. Philippe, A. Bommarius, K. Drauz, H.-P. Krimmer, Degussa AG, Germany. **2002**, p. 28; d) S. K. Cheng, S. Y. Zhang, P. A. Wang, Y. Q. Kuang, X. L. Sun, *Appl. Organomet. Chem.* **2005**, *19*, 975 – 979.

[12] a) A. P. Krapcho, Z. Getahun, *Synth. Commun.* **1985**, *15*, 907 – 910; b) M. H. Norman, J. L. Kelley, E. B. Hollingsworth, *J. Med. Chem.* **1993**, *36*, 3417 – 3423.

[13] a) J. Van der Louw, C. M. D. Komen, A. Knol, F. J. J. De Kanter, J. L. Van der Baan, F. Bickelhaupt, G. W. Klumpp, *Tetrahedron Lett.* **1989**, *30*, 4453 – 4456; b) J. Van der Louw, J. L. Van der Baan, F. J. J. De Kanter, F. Bickelhaupt, G. W. Klumpp, *Tetrahedron* **1992**, *48*, 6087 – 6104.

[14] L. F. Tietze, M. A. Duefert, T. Hungerland, K. Oum, T. Lenzer, *Chem. Eur. J.* **2011**, *17*, 8452 – 8461.

[15] C. A. McNamara, F. King, M. Bradley, *Tetrahedron Lett.* **2004**, *45*, 8527 – 8529.

[16] a) L. Cheng, L. Liu, D. Wang, Y.-J. Chen, *Org. Lett.* **2009**, *11*, 3874 – 3877; b) H. Chen, R. Jiang, Q.-F. Wang, X.-L. Sun, S.-Y. Zhang, *Acta Chim. Slov.* **2009**, *56*, 694 – 697.

[17] A. Iuliano, C. Lecci, P. Salvadori, *Tetrahedron: Asymmetry* **2003**, *14*, 1345 – 1353.

[18] G. Ghini, L. Lascialfari, C. Vinattieri, S. Cicchi, A. Brandi, D. Berti, F. Betti, P. Baglioni, M. Mannini, *Soft Matter* **2009**, *5*, 1863 – 1869.

[19] S. Löber, P. Rodriguez-Loaiza, P. Gmeiner, *Org. Lett.* **2003**, *5*, 1753 – 1755.

[20] A. K. Oyelere, P. C. Chen, L. P. Yao, N. Boguslavsky, *J. Org. Chem.* **2006**, *71*, 9791 – 9796.

[21] F. Gaggini, A. Porcheddu, G. Reginato, M. Rodriquez, M. Taddei, *J. Comb. Chem.* **2004**, *6*, 805 – 810.

[22] F. Galindo, B. Altava, M. I. Burguete, R. Gavara, S. V. Luis, *J. Comb. Chem.* **2004**, *6*, 859 – 861.

[23] Thanks to the quantitative recovery of the polymer materials and the relatively high mass amount of anchored chiral derivative, this choice provides a procedure that is both fast and reliable.

[24] In addition, the nature of the alkaloid derivative appears to affect to some extent the solubility of the copper salt catalyst in the reaction medium. In particular, mixing CuI, DIPEA, and **10**, **11**, **12**, or **14** in CH_2Cl_2 afforded a clear solution in less than 15 min. On the contrary, when the anthraquinone derivative **13** was used the copper salt remained partially undissolved even after 30 min stirring.

[25] D. Cancogni, A. Mandoli, R. P. Jumde, D. Pini, *Eur. J. Org. Chem.* **2012**, 1336 – 1345.

[26] Control experiments (see the Supporting Information) confirmed the lack of any enantioselective catalytic activity in the solution.

[27] a) M. A. Calter, X. Guo, *J. Org. Chem.* **1998**, *63*, 5308 – 5309; b) M. A. Calter, F. C. Bi, *Org. Lett.* **2000**, *2*, 1529 – 1531; c) M. A. Calter, X. Guo, W. Liao, *Org. Lett.* **2001**, *3*, 1499 – 1501; d) M. A. Calter, W. Song, J. G. Zhou, *J. Org. Chem.* **2004**, *69*, 1270 – 1275.

[28] 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.

[29] The dimerization of methylketene is probably the most synthetically useful transformation in the chemistry under study, as it affords an enantioenriched building block amenable of selective elaboration into di- and polypropionate units (see Ref. [27]). Nonetheless, on response to a referee request we examined the reaction scope more in depth, by using **P9** (Alk = QD) to promote the heterogeneous asymmetric dimerization of two additional acid chlorides provided with ester or aromatic moieties. The results of these experiments (see the Supporting Information) provided somewhat reduced chiral induction (71–74% *ee*).

[30] a) O. Gleeson, G.-L. Davies, A. Peschiulli, R. Tekoriute, Y. K. Gun'ko, S. J. Connon, *Org. Biomol. Chem.* **2011**, *9*, 7929 – 7940; b) J. Hong, F. Zaera, *J. Am. Chem. Soc.* **2012**, *134*, 13056 – 13065; c) K. A. Fredriksen, T. E. Kristensen, T. Hansen, *Beilstein J. Org. Chem.* **2012**, *8*, 1126 – 1133.

[31] F. Balzano, R. P. Jumde, A. Mandoli, S. Masi, D. Pini, G. Uccello-Barretta, *Chirality* **2011**, *23*, 784 – 795.

[32] M. A. Calter, *J. Org. Chem.* **1996**, *61*, 8006 – 8007.

[33] H. Li, X. Liu, F. Wu, L. Tang, L. Deng, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20625 – 20629.

[34] T. Bui, M. Borregan, C. F. Barbas, *J. Org. Chem.* **2009**, *74*, 8935 – 8938.

[35] Y. Chen, S.-K. Tian, L. Deng, *J. Am. Chem. Soc.* **2000**, *122*, 9542 – 9543.

[36] a) S. Itsuno, Y. Sakurai, K. Ito, T. Maruyama, S. Nakahama, J. M. J. Frechet, *J. Org. Chem.* **1990**, *55*, 304 – 310; b) S. Itsuno, I. Moue, K. Ito, *Chem. Commun.* **1991**, 1599 – 1601.

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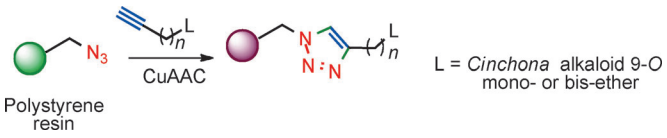

Thank you for your support: Effective procedures are described for the preparation of supported organocatalysts by the copper-catalyzed Huisgen cycloaddition addition between alkyne-functionalized alkaloid derivatives and gel-type azidomethylpolystyrene.

Supported Catalysts

*Ravindra P. Jumde, Anila Di Pietro, Antonella Manariti, Alessandro Mandoli**

■■ – ■■

New Polymer-Supported Mono- and Bis-*Cinchona* Alkaloid Derivatives: Synthesis and Use in Asymmetric Organocatalyzed Reactions