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# Supported and Unsupported Chiral Squaramides as Organocatalysts for Stereoselective Michael Additions. Synthesis of Enantiopure Chromenes and Spirochromanes

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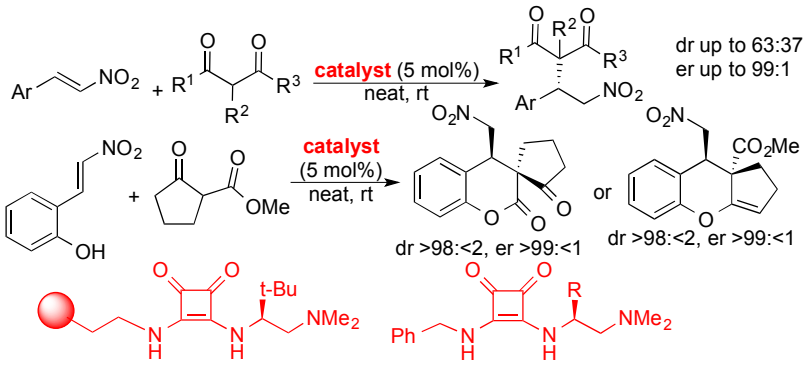



**Abstract**.

Novel supported chiral bifunctional squaramides have been easily prepared starting from diamines derived from natural amino acids and commercially available aminoalkyl polystyrene resins. These squaramides behave as excellent stereoselective recoverable organocatalysts in different Michael additions, in neat conditions at room temperature. The reaction on 2-(2-nitrovinyl) phenol as electrophile lead, in excellent yields and enantioselectivities, to intermediates that can be easily transformed into 4*H*-chromenes, and spirochromanones.

**Key words**: Asymmetric synthesis. Chromenes. Michael addition. Organocatalysis. Supported squaramides. Squaramides

**Introduction**.

The first chiral bifunctional squaramide derived from cinchonine was prepared a decade ago, and successfully used in the enantioselective nitro-Michael reaction.[1] Since then, a lot of squaramides, specially derived from cinchone alkaloids or *trans*-1,2-cyclohexane diamine, have been synthesized and used as organocatalysts in different enantioselective transformations.[2] Additionally, a few squaramides with a common 3,5-*bis*(trifluoromethyl) aniline and a chiral diamine derived from α-amino acids have been described as excellent catalysts for different Michael additions,[3] and tandem reactions leading to complex structures.[4]

The easy recovering of the catalyst is a mandatory fact for its practical application, and the support onto a solid material is a good way to solve that problem. In spite of the high volume of reports of novel squaramides, only a few antecedents have been directed to the preparation and use of that kind of supported organocatalysts. The first supported catalyst (**I**) was prepared by click-chemistry grafting methodology of an elaborated *trans*-1,2-cyclohexane diamine-derived squaramide onto polystyrene resin, and successfully used in batch,[5] and continuous flow[6] nitro-Michael additions.

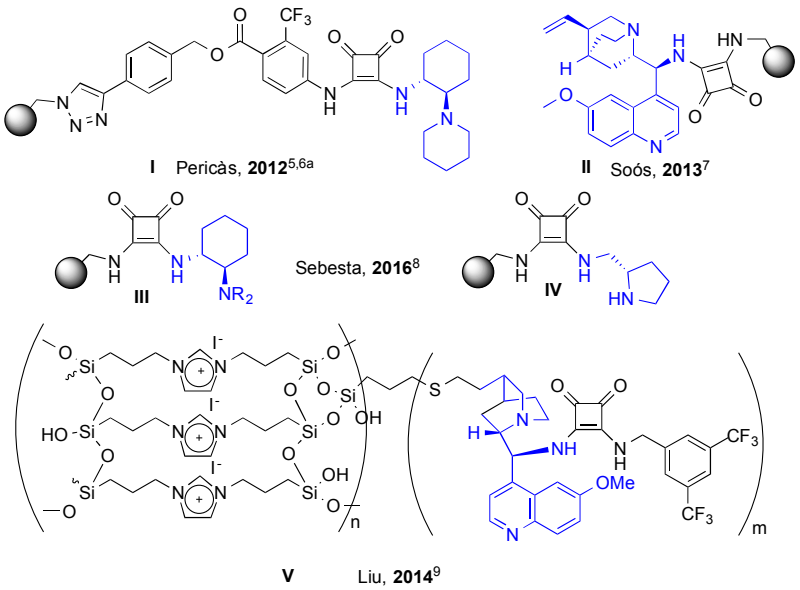



**Figure 1**. Supported squaramides previously described.

In parallel, a shorter synthesis of catalyst (**II**) was described by support of quinine-derived squaramide onto aminomethyl polystyrene,[7] and very recently, the same resin has been used as support for squaramides derived from *trans*-1,2-cyclohexane diamine (**III**), and 2-methylamino pyrrolidine (**IV**).[8] A highly active heterogeneous catalyst (**V**) was also prepared by immobilization of an squaramide derived from cinchonidine onto an hybrid silica functionalized with imidoazolium groups[9] (Figure 1).

As a part of a project directed to the synthesis of different organocatalysts, we have previously described supported prolinamides,[10] and ureas and thioureas onto different polystyrene resins,[11] or obtained by co-polymerization of monomeric thioureas with styrene and divinylbenzene.[12] Now we have addressed the preparation of highly efficient and recoverable bifunctional squaramides, taking into account that the synthesis must be as short as possible and starting from cheap commercially available materials which allow the access to both enantiomers of the catalysts.

This idea led us to consider the two-steps synthesis of these materials starting from different aminoalkyl polystyrenes as support, and bifunctional chiral squaramides obtained by reaction of diethyl squarate and chiral diamines derived from natural amino acids (Figure 2).

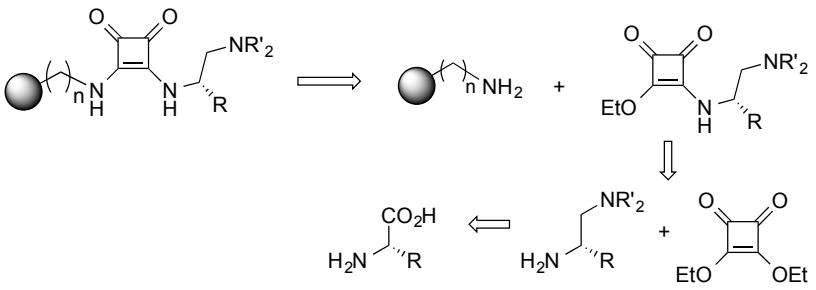
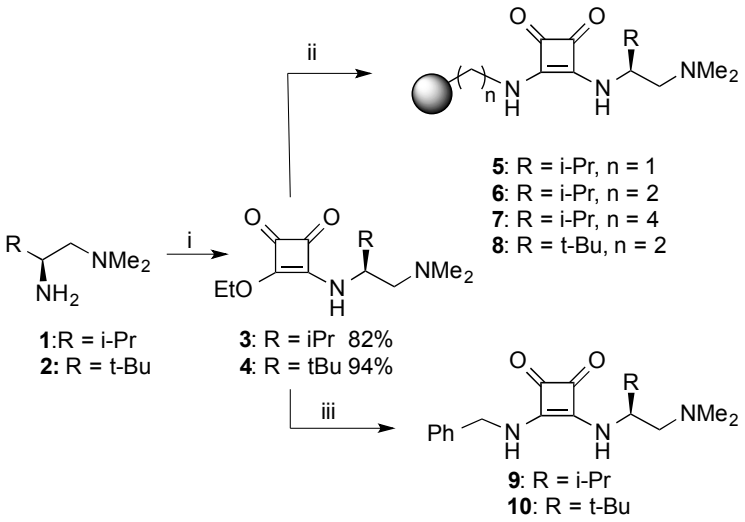



**Figure 2**. Proposed retrosynthetic analysis of the supported squaramides.

**Results and discussion**.

Four supported (**5-8**) and two unsupported (**9-10**) squaramides were prepared as summarized in Scheme1 from semi-squaramides **3** and **4** obtained, in very good yields, by condensation of diethyl squarate and diamines **1** and **2** derived from *L*-valine or *L-tert*-leucine respectively.[13] Immobilized materials **5-7**, which differ in the length of the tether linking the squaramide and the solid support, were prepared by reaction of **3** with methylamino-, ethylamino-, and butylamino-polystyrene resins respectively. Supported squaramide **8**, with a bulkier substituent at the stereogenic center, was also obtained from **4** and aminoethyl-polystyrene. Analytical data shown that the incorporation of the monomers to the resins occurred in quantitative yields, and that the effective functionalization (*f*) varies from 0.86 to 0.96 (Table 1, entries 1-4). All these materials shown characteristic IR bands at 3250, 1795, and 1688 $cm^{-1}$. For comparative purposes, unsupported squaramides **9** and **10** were also obtained, in very good yields, by reaction of benzyl amine with **3** and **4** respectively (Table 1, entries 5, 6).




**Scheme 1**. Synthesis of supported and unsupported squaramides.

**Table 1**. Supported and unsupported squaramides prepared in this work.

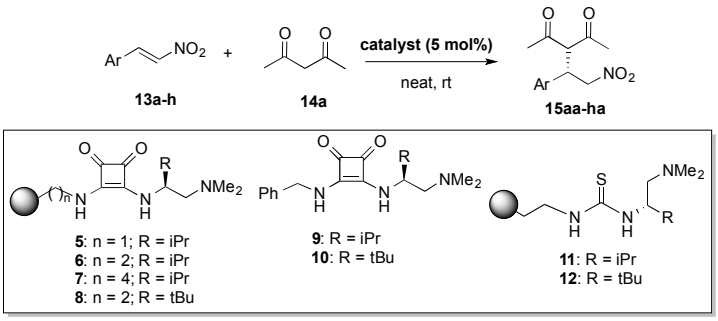
| Entry | Squaramide | R | n | Yield (%)[a] | *f*[b] | *f/fmax* |
|---|---|---|---|---|---|---|
| 1 | **5** | i-Pr | 1 | 94 | 0.96 | 100 |
| 2 | **6** | i-Pr | 2 | 90 | 0.86 | 100 |
| 3 | **7** | i-Pr | 4 | 80 | 0.94 | 100 |
| 4 | **8** | t-Bu | 2 | 81 | 0.87 | 100 |
| 5 | **9** | i-Pr | - | 80[c] | - | - |
| 6 | **10** | t-Bu | - | 85[c] | - | - |

[a] Yields were calculated as a ratio of the mass of the starting and final product. [b] Determined from the analytical data of the nitrogen atom in the polymers. [c] Yields of isolated pure compounds.

The activity of all the squaramides was studied in the addition of different nucleophiles to β-substituted nitroolefins. The addition of acetylacetone (**14a**) to *trans*-β-nitrostyrene (**13a**) was initially selected as a model to compare the activity and the length of the tether of the supported catalysts **5-8** with the homogeneous squaramides **9**, **10**. To this end, *trans*-β-nitrostyrene was reacted with two equivalents of 2,4-pentanedione, at room temperature without solvent, in the presence of 5 mol% of catalysts **5**-**10**, and the results are collected in Table 2 (entries 1-9).

The summarized results shown that all the catalysts were very active, leading to the addition product **15aa** in excellent yields and enantioselection, but the *tert*-butyl-substituted homogeneous squaramide **10** was slight more active than its homologous *iso*-propyl derivative **9** (compare entries 1, 2 in Table 2). The loading of catalyst can be reduced to 2 mol% (entry 3) or 0.5 mol% (entry 4) without loss in the yield and enantioselection, and the reaction can be scaled up to 6 mmol without loss of enantioselectivity (entry 5). It is also noteworthy that the length of the spacer, in the supported catalysts, play only a little influence in the reaction (entries 6-9 in Table 2), but the better results were obtained for supported squaramides derived from ethylamino polystyrene **6** and **8**.

**Table 2**. Reaction of different nitroolefins with acetylacetone catalyzed by squaramides and thioureas.




| Entry[a] | Ar | Catalyst | Time (h) | Product (Yield)[b] | Er[c] (Configuration) |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | **9** | 2 | **15aa** (80) | 97:3 (S) |
| 2 | $C_6H_5$ | **10** | 0.5 | **15aa** (92) | 99:1 (S) |
| 3 | $C_6H_5$ | **10**[d] | 1 | **15aa** (82) | 99:1 (S) |
| 4 | $C_6H_5$ | **10**[e] | 2 | **15aa** (89) | 99:1 (S) |
| 5 | $C_6H_5$ | **10**[e,f] | 2 | **15aa** (70) | 99:1 (S) |
| 6 | $C_6H_5$ | **5** | 2 | **15aa** (89) | 97:3 (S) |
| 7 | $C_6H_5$ | **6** | 2 | **15aa** (80) | 98:2 (S) |
| 8 | $C_6H_5$ | **7** | 2 | **15aa** (88) | 96:4 (S) |
| 9 | $C_6H_5$ | **8** | 1 | **15aa** (97) | 99:1 (S) |
| 10 | $C_6H_5$ | **8**[e] | 2 | **15aa** (96) | 96:4 (S) |
| 11 | $C_6H_5$ | **8**[e,f] | 16 | **15aa** (74) | 92:8 (S) |
| 12 | $C_6H_5$ | **11** | 1 | **15aa** (74) | 87:13 (S) |
| 13 | $C_6H_5$ | **12** | 1 | **15aa** (70) | 81:19 (S) |
| 14 | p-$ClC_6H_4$ | **10** | 1.5 | **15ba** (88) | 99:1 (S) |
| 15 | p-$ClC_6H_4$ | **8** | 2 | **15ba** (80) | 97:3 (S) |
| 16 | p-$CF_3C_6H_4$ | **10** | 1 | **15ca** (76) | >99:<1 (S) |
| 17 | p-$CF_3C_6H_4$ | **8** | 1.5 | **15ca** (78) | 99:1 (S) |
| 18 | o-$NO_2C_6H_4$ | **10** | 1 | **15da** (87) | 98:2 (S) |

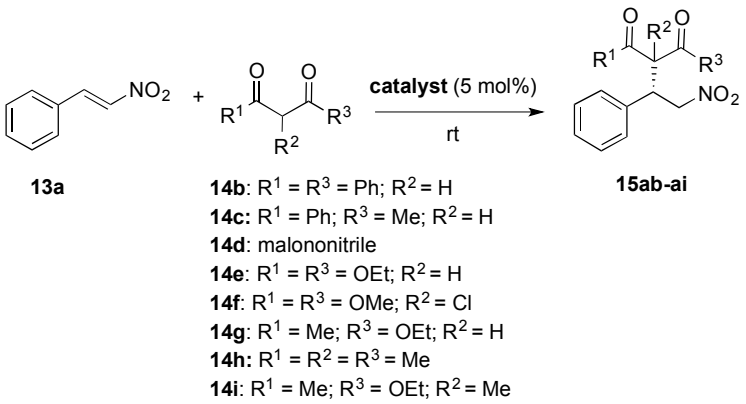
| | | | | | |
|---|---|---|---|---|---|
| 19 | o-$NO_2C_6H_4$ | **8** | 1.5 | **15da** (88) | 99:1 (S) |
| 20 | p-$MeOC_6H_4$ | **10** | 1.5 | **15ea** (95) | 98:2 (S) |
| 21 | p-$MeOC_6H_4$ | **8** | 2 | **15ea** (86) | 99:1 (S) |
| 22 | 1-naphthyl | **10** | 1 | **15fa** (75) | 99:1 (S) |
| 23 | 1-naphthyl | **8** | 2 | **15fa** (90) | 99:1 (S) |
| 24 | 2-naphthyl | **10** | 1.5 | **15ga** (85) | 97:3 (S) |
| 25 | 2-naphthyl | **8** | 2.5 | **15ga** (83) | 95:5 (S) |
| 26 | 2-furyl | **10** | 1 | **15ha** (77) | 97:3 (S) |
| 27 | 2-furyl | **8** | 1 | **15ha** (84) | 96:4 (S) |

[a] The reactions were carried out at 0.3 mmol scale with 2 fold excess of acetylacetone without solvent, at rt. [b] Numbers in parenthesis correspond to isolated products after flash chromatography. [c] Determined by chiral HPLC. [d] Only 2 mol% of catalyst was used in this reaction. [e] Only 0.5 mol% of catalyst was used in this reaction. [f] The reaction was scaled up to 6 mmol, and the yield refers to pure compound obtained after recrystallization.

Additionally, the results obtained with squaramide **8** were very similar to those provided by its homolog unsupported squaramide **10**, indicating that the anchorage of the active structure does not modify the activity of the catalysts (compare entries 2 *versus* 9 in Table 2). Only an slight longer reaction times were observed for the reactions promoted by the supported catalyst. Squaramide **8** also worked very well with a catalyst loading of 0.5 mol% (entry 10), and when the reaction was scaled up to 6 mmol, although increasing the reaction time (entry 11 in Table 2). For comparative purposes, supported thioureas **11** and **12**[14] were also tested as catalysts in the same reaction conditions, but the reaction occurred in much lower enantioselection (entries 12, 13).

Supported catalyst **8** was next used in the conjugate addition of 2,4-pentane dione **14a** to different β-aryl-substituted nitroolefins (**14b-h**) under the described reaction conditions (entries 14-27 in Table 2). The Michael adducts (**15ba-15ha**) were isolated in very good yields and excellent enantioselectivities in short reaction times. The position or the electronic character of the substituents at the phenyl group play only negligible effect on the yield of the reaction, and only slight decrease in the enantioselectivity was observed in the reactions of 2-naphthyl- (**15g**) or 2-furyl-substituted (**15h**) nitroolefins (entries 24, 27 in Table 2).

The study was first extended to the reaction of different acyclic nucleophiles (**14b-i)** with *trans*-β-nitrostyrene by using the most active catalysts in the described reaction conditions except when both reactants were solid. In those cases, DCM was used as a solvent (Scheme 2, and Table 3).




**13a**

**14b**: $R^1 = R^3 = Ph$; $R^2 = H$
**14c:** $R^1 = Ph$; $R^3 = Me$; $R^2 = H$
**14d**: malononitrile
**14e**: $R^1 = R^3 = OEt$; $R^2 = H$
**14f**: $R^1 = R^3 = OMe$; $R^2 = Cl$
**14g**: $R^1 = Me$; $R^3 = OEt$; $R^2 = H$
**14h:** $R^1 = R^2 = R^3 = Me$
**14i**: $R^1 = Me$; $R^3 = OEt$; $R^2 = Me$

**15ab-ai**

**Scheme 2**. Addition of different acyclic nucleophiles to nitrostyrene.

Both homogeneous (**10**) and heterogeneous (**8**) catalysts promote the addition of dibenzoylmethane (**14b**) and benzoylacetone (**14c**) to *trans*-β-nitrostyrene in very good yields and enantioselectivities (entries 1, 2 and 5, 6 in Table 3). The reaction can be carried without solvent under ball-milling conditions, maintaining both the yield and enantioselection (entry 3 in Table 3). The reaction failed when malononitrile (**14d**) was used as nucleophile, because the addition product **15ad** was isolated in moderate yield and poor enantioselectivity (entries 7, 8 in Table 3).

The less acidic diethyl malonate (**14e**) also reacted very slowly, in neat conditions, yielding the addition product (**15ae**) in low yield, although moderate enantioselectivity (entry 9). Dimethyl 2-chloro malonate (**14f**) reacted faster than **14e**, leading to **15af** in good yield and enantioselectivity when the reaction was catalyzed **10** (entry 10), but very poor enantioselection in the presence of **8** (entry 11 in Table 3). On the contrary, the reaction of ethyl 3-oxo-butyrate (**14g**) with *trans*-β-nitrostyrene occurred easily, yielding **15ag** in good yield, moderate diastereoselection but excellent enantioselectivity (entries 12, 13 in Table 3).

**Table 3**. Reaction of *trans*-β-nitrostyrene (**13a**) with different acyclic nucleophiles catalyzed by squaramides **6**, **8**, **10**.[a]

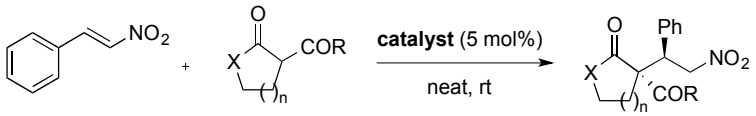
| Entry | Reagent | Catalyst | Time (h) | Solvent | Product (Yield)[b] | dr[c] | er[d] (Config) |
|---|---|---|---|---|---|---|---|
| 1 | **14b** | **10** | 48 | $CH_2Cl_2$ | **15ab** (82) | - | 94:6 (*S*) |
| 2 | **14b** | **8** | 24 | $CH_2Cl_2$ | **15ab** (73) | - | 91:9 (*S*) |
| 3[e,f] | **14b** | **10** | 72 | neat | **15ab** (75) | - | 91:9 (*S*) |
| 4[e] | **14b** | **6** | 17 | $CH_2Cl_2$ | **15ab** (80) | - | 82:18 (*S*) |
| 5 | **14c** | **10** | 8 | $CH_2Cl_2$ | **15ac** (86) | 60:40 | 96:4 (*S, S*) (95:5) (*R, S*) |
| 6 | **14c** | **8** | 8 | $CH_2Cl_2$ | **15ac** (96) | 61:39 | 94:6 (*S, S*) (93:7) (*R, S*) |
| 7 | **14d** | **10** | 6 | $CH_2Cl_2$ | **15ad** (67) | - | 60:40 (*S*) |
| 8 | **14d** | **8** | 9 | $CH_2Cl_2$ | **15ad** (47) | - | 52:48 (*S*) |
| 9 | **14e** | **10** | 120 | neat | **15ae** (40)[g] | - | 83:17 (*S*) |
| 10 | **14f** | **10** | 3 | neat | **15af** (82) | - | 85:15 (*S*) |
| 11 | **14f** | **8** | 18 | neat | **15af** (75) | - | 65:35 (*S*) |
| 12 | **14g** | **10** | 1 | neat | **15ag** (73) | 63:37 | 98:2 (*S, S*) (97:3) (*S, R*) |
| 13 | **14g** | **8** | 2 | neat | **15ag** (78) | 62:38 | 96:4 (*S, S*) (94:6) (*S, R*) |
| 14 | **14h** | **10** | 17 | neat | **15ah** (89) | - | 99:1 (*R*) |
| 15 | **14h** | **6** | 86 | neat | **15ah** (53)[g] | - | 96:4 (*R*) |
| 16 | **14h** | **8** | 120 | neat | **15ah** (45)[g] | - | 98:2 (*R*) |
| 17 | **14i** | **10** | 24 | neat | **15ai** (70) | 62:38 | 92:8 (*R, R*) (94:6) (*S, R*) |
| 18 | **14i** | **8** | 54 | neat | **15ai** (74) | 58:42 | 83:17 (*R, R*) (94:6) (*S, R*) |

[a] The reactions were carried out at 0.3 mmol scale with 2 fold excess of nucleophile, at rt. [b] Numbers in parenthesis correspond to isolated products after flash chromatography. [c] Determined by $^1$HNMR in the reaction mixtures. [d] Determined by chiral HPLC, and numbers in parenthesis correspond to the er of the minor diastereoisomers. [e] Only 1.5 excess of nucleophile was used in these reactions. [f] The reaction was carried out under ball-milling conditions. [g] The values given do not correspond to yields, but to conversions, and were determined by $^1$HNMR of the reaction mixtures.

Tertiary pronucleophile 3-methyl-2,4-pentanedione (**14h**) reacted slower than unsubstituted diketone **14a**, in the presence of homogeneous squaramide **10** although maintaining good yield and excellent enantioselection (compare entry 14 in Table 3 *versus* entry 2 in Table 2). Supported catalysts **6** and **8** were also able to promote the same addition reaction maintaining the good enantioselectivity, but at expenses of increasing the reaction time and diminishing the yield (entries 15, 16 in Table 3). The same fact was observed for the reaction of ethyl 2-methyl-3-oxo-butyrate (**14i**) with respect to the unsubstituted homolog **14g**. In both cases the yields and stereoselectivities were quite similar, but in much longer reaction time (compare entries 17, 18 *versus* 12, 13 in Table 3).

It is interesting to note that the enantioselection in the addition process was generally very good, but the diastereoselectivity was moderate (ca. 3:2) when prochiral substrates (**14c**, **g**, **i**) were used as nucleophiles. This fact is in agreement with previously reported results.[5, 7]

Prochiral cyclic β-difunctionalized substrates also act as nucleophiles in the addition reaction, but the reactivity and stereochemical behavior are highly dependent on their structure (Scheme 3).




**Scheme 3**. Addition of different cyclic nucleophiles to *trans*-β-nitrostyrene.

**Table 4**. Michael additions of cyclic nucleophiles to *trans*-β-nitrostyrene.[a]

| Entry | Reagent | Catalyst | Time (h) | Product (Yield)[b] | *Anti:syn*[c] | Er (anti)[d] |
|---|---|---|---|---|---|---|
| 1 | **16a** | **9** | 1 | **17aa** (92) | >98:<2 | 99:1 |
| 2 | **16a** | **10** | 2 | **17aa** (90) | >98:<2 | 98:2 |
| 3 | **16a** | **5** | 6 | **17aa** (82) | >98:<2 | 99:1 |
| 4 | **16a** | **6** | 2 | **17aa** (88) | >98:<2 | 98:2 |
| 5 | **16a** | **7** | 4 | **17aa** (80) | >98:<2 | >99:<1 |
| 6 | **16a** | **8** | 3 | **17aa** (85) | >98:<2 | >99:<1 |
| 7 | **16b** | **9** | 48 | **17ab** (58)[e] | >98:<2 | 98:2 |
| 8 | **16b** | **10** | 48 | **17ab** (82) | >98:<2 | 98:2 |
| 9 | **16b** | **6** | 96 | **17ab** (77) | >98:<2 | 98:2 |
| 10 | **16c** | **10** | 8 | **17ac** (98) | >98:<2 | >99:<1 |
| 11 | **16c** | **6** | 22 | **17ac** (76) | >98:<2 | >99:<1 |
| 12 | **16d** | **10** | 2 | **17ad** (94) | 82:18 | >99:<1 |
| 13 | **16d** | **8** | 5 | **17ad** (96) | 85:15 | 98:2 |
| 14 | **16e** | **10** | 1.5 | **17ae** (80) | 56:44 | >99:<1 (97:3)[f] |
| 15 | **16e** | **8** | 40 | **17ae** (72) | 53:47 | 92:8 (92:8)[f] |

[a] The reactions were carried out at 0.3 mmol scale with 2 fold excess of nucleophile, at rt. [b] Numbers in parenthesis correspond to isolated products after flash chromatography. [c] Determined by $^1$HNMR in the reaction mixtures. [d] Determined by chiral HPLC, and numbers in parenthesis correspond to the er of the minor diastereoisomers. [e] 40% of unreacted nitrostyrene was recovered from the reaction mixture. [f] numbers in parenthesis correspond to the er for the *syn* diastereoisomer.

The influence of the nature of the functional groups and the size of the cyclic structure was tested by using as nucleophiles 2-alkoxycarbonyl substituted cycloalkanones **16a-c**, that differ in the size of the ketone, and 2-acetyl cyclopentanone (**16d**) and 2-acetyl butyrolactone (**16e**). The process was studied by reacting *trans*-β-nitrostyrene with

two equivalents of nucleophile and 5 mol% of catalysts at room temperature in neat conditions (Table 4).

Fortunately, both homogeneous (**9**, **10**) and supported (**5**-**8**) squaramides were able to promote the addition of **16a** to **13a** in very good yields and excellent enantioselection, leading to **17aa** as a single nearly enantiopure diastereoisomer (entries 1-6 in Table 4). The only differences observed was that the reactions promoted by supported or *tert*-Leucine-derived catalysts were slight slower than those catalyzed by homogeneous or Valine-derived ones.

Cycloheptanone derivative **16c** easily added to *trans*-β-nitrostyrene in the presence of homogeneous (**10**) or supported (**6**) catalysts leading to **17ac** in good yields and total stereoselectivity (entries 10, 11 in Table 4). On the contrary, 2-ethoxycarbonyl cyclohexanone **16b** showed to be much less reactive than its homologs, although the reaction occurred with excellent stereoselection (compare entries 7-9 *versus* 1, 2, 4 in Table 4). To our surprise, the supported catalyst **8** was not able to promote the reaction of **16b** with *trans*-β-nitrostyrene, in the described conditions, and the starting reagents were recovered unchanged after 96 h.

2-Acetyl cyclopentanone **16d** easily reacted with *trans*- β-nitrostyrene in the presence of catalysts **8** and **10**, leading to the addition product **17ad** in excellent yield and enantioselectivity, but moderate diastereoselection (entries 12, 13 in Table 4). Finally, 2-acetyl butyrolactone **16e** quickly reacted catalyzed by homogeneous **10**, but slowly in the presence of supported catalyst **8**. In both cases the level of enantioselection was maintained although **17ae** was obtained as a near equimolar mixture of diastereoisomers (entries 14, 15 in Table 4).

The recovering and reusing of the catalysts were studied for supported catalysts **6** and **8** in the addition of 2,4-pentanedione (**14a**), and 2-ethoxycarbonyl cyclopentanone (**16a**) to *trans*-β-nitrostyrene. The recycling experiments were done in neat conditions, at room temperature, with 5 mol% of catalysts. The reaction time was maintained constant in each cycle (1 h. for the reaction of **13a** with **14a**; 3h. for the addition of **16a** to **13a** in the presence of **8**, and 2h. for the same reaction catalyzed by **6**), and the results are collected in Table 5. The catalyst was recovered after each cycle by filtration, washed with DCM, dried, and reused in the next cycle. To our delight, both the diastereo- and enantioselection were maintained along all the cycles.

$^1$HNMR spectra of the reaction mixtures showed total conversion, and only a very slight deterioration in the activity was observed for catalyst **8** in the last cycle of the reaction between **13a** and **14a** (98%). It is also very important to note that 84-98% of catalyst was recovered by filtration in each cycle, and that no appreciable leaching was observed, because the analytical data of catalyst **8** shown the same effective functionalization after six cycles than the starting material (*f* = 0.85 *versus* 0.87 in entry 4 in Table 1).

**Table 5**. Recyclability of supported catalysts **6** and **8** in the reactions of **13a** with **14a** and **16a**.

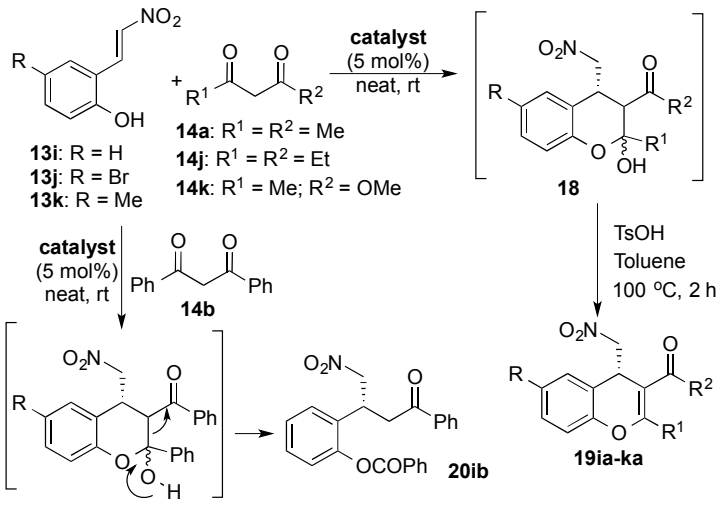
| Entry | Cycle | Reagents | Catalyst Recovered (%)[a] | Time (h) | Product (Yield)[b] | dr[c] | er[d] |
|---|---|---|---|---|---|---|---|
| 1 | 1 | **13a/14a** | **8** | 1 | **15aa** (97) | - | 99:1 |
| 2 | 2 | **13a/14a** | **8** (86) | 1 | **15aa** (92) | - | >99:<1 |
| 3 | 3 | **13a/14a** | **8** (84) | 1 | **15aa** (96) | - | 98:2 |
| 4 | 4 | **13a/14a** | **8** (92) | 1 | **15aa** (94) | - | >99:<1 |
| 5 | 5 | **13a/14a** | **8** (88) | 1 | **15aa** (94) | - | 98:2 |
| 6 | 6 | **13a/14a** | **8** (87) | 1 | **15aa** (89) | - | 98:2 |
| 7 | 1 | **13a/16a** | **8** | 3 | **17aa** (85) | >98:<2 | 99:1 |
| 8 | 2 | **13a/16a** | **8** (85) | 3 | **17aa** (86) | >98:<2 | 99:1 |
| 9 | 3 | **13a/16a** | **8** (84) | 3 | **17aa** (82) | >98:<2 | 99:1 |
| 10 | 4 | **13a/16a** | **8** (98) | 3 | **17aa** (83) | >98:<2 | 98:2 |
| 11 | 5 | **13a/16a** | **8** (85) | 3 | **17aa** (80) | >98:<2 | 98.5:1.5 |
| 12 | 6 | **13a/16a** | **8** (98) | 3 | **17aa** (85) | >98:<2 | 98:2 |
| 13 | 1 | **13a/16a** | **6** | 2 | **17aa** (88) | >98:<2 | 98:2 |
| 14 | 2 | **13a/16a** | **6** (85) | 2 | **17aa** (84) | >98:<2 | 98:2 |
| 15 | 3 | **13a/16a** | **6** (84) | 2 | **17aa** (86) | >98:<2 | 98:2 |
| 16 | 4 | **13a/16a** | **6** (85) | 2 | **17aa** (86) | >98:<2 | 98:2 |
| 17 | 5 | **13a/16a** | **6** (98) | 2 | **17aa** (87) | >98:<2 | 98:2 |

[a] Numbers in parenthesis refer to the amount of catalyst recovered after each cycle. [b] Numbers in parenthesis to isolated compounds after flash chromatography. [c] Determined by HNMR in the reaction

mixture, and the values means that a single diastereoisomer was detected. [d] Determined by Chiral HPLC.

Aimed by the results described above, we envisaged that the use of *orto*-substituted nitroolefins derived from phenol as electrophiles gave intermediates that could be able to participate in subsequent annulation leading to hemiacetals easily transformed into chromenes or related derivatives. Benzopyran and related framework can be found in many types of natural and biological active compounds,[15] and the organocatalytic stereoselective synthesis of that kind of compounds has recently received some attention,[16] but there are no antecedents on the use of supported catalysts in that transformation. To that end, we reacted 2-(2-nitrovinyl) phenol derivatives (**13i-k**) with different pro-nucleophiles (**14a**, **b**, **j**, **k**) in the presence of supported squaramide (**8**), and unsupported one (**10**) for comparative purposes (Scheme 4 and Table 6).

The reaction of *trans*-2-hydroxy-β-nitrostyrene **13i** with acetylacetone (**14a**), in neat conditions at rt, and 5 mol% of thiourea **10** was completed after 1 h, but hemiacetal (**18**) was obtained as a mixture of diastereoisomers. To avoid that problem, the reaction mixture was directly dehydrated by heating at 100 $^{o}$C for 2 h with catalytic PTSA,[16b] leading to 4*H*-chromene **19ia** in excellent yield (93%), and near total enantioselection (er 99:1) (entry 1 in Table 6). In the same conditions, the reaction promoted by supported squaramide **8** was slower (14h), leading to **19ia** in lower, although acceptable, yield (72%), but maintaining the excellent level of enantioselectivity (er 97:3) (entry 2 in Table 6).




**Scheme 4**. Sequential nitro-Michael, hemiacetalization, dehydration to 4*H*-chromenes.

**Table 6**. One-pot enantioselective synthesis of 4*H*-chromenes.[a]

| Entry | Reagents | Catalyst | t (h)[b] | Product (Yield)[c] | Er[d] (Configuration) |
|---|---|---|---|---|---|
| 1 | **13i/14a** | **10** | 1 | **19ia** (93) | 99:1 (S) |
| 2 | **13i/14a** | **8** | 14 | **19ia** (72) | 97:3 (S) |
| 3 | **13i/14b** | **10** | 3 | **20ib** (80) | 93:7 (R) |
| 4 | **13i/14b** | **8** | 9 | **20ib** (78) | 62:38 (R) |
| 5 | **13i/14j** | **10** | 1 | **19ij** (84) | 99:1 (S) |
| 6 | **13i/14j** | **8** | 14 | **19ij** (65) | 96:4 (S) |
| 7 | **13i/14k** | **10** | 1 | **19ik** (72) | >99:<1 (S) |
| 8 | **13i/14k** | **8** | 24 | **19ik** (60) | 97:3 (S) |
| 9 | **13j/14a** | **10** | 1 | **19ja** (82) | 99:1 (S) |
| 10 | **13j/14a** | **8** | 14 | **19ja** (70) | 97:3 (S) |
| 11 | **13k/14a** | **10** | 1 | **19ka** (77) | >99:<1 (S) |
| 12 | **13k/14a** | **8** | 14 | **19ka** (67) | 96:4 (S) |

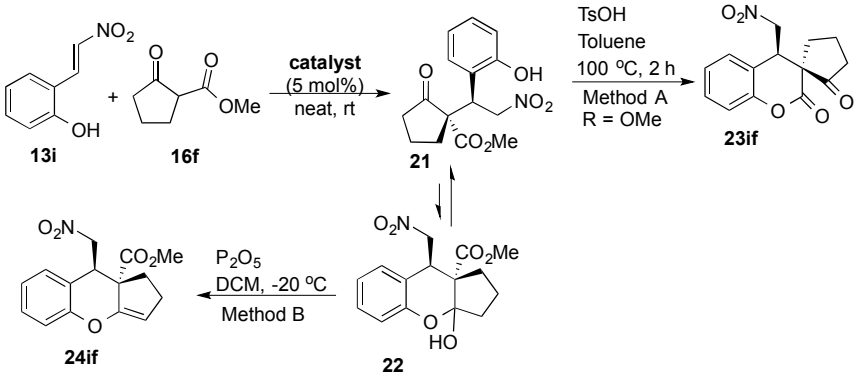
[a] The reactions were carried out at 0.3 mmol scale with 2 fold excess of nucleophile at rt. [b] Reaction times refer to the Michael addition step. [c] Numbers in parenthesis correspond to isolated products after flash chromatography. [d] Determined by chiral HPLC.

Similar results were obtained when 3,5-heptanedione (**14j**) or methyl acetoacetate (**14k**) were used as nucleophiles in the reactions catalyzed by **8** or **10**. The addition-hemiacetalization-elimination products **19ij** and **19ik** were obtained in good yields and total enantioselection (entries 5-8 in Table 6). A drastic change in the reaction was observed for dibenzoylmethane (**14b**) as pronucleophile. In the described reaction conditions, compound **20ib** was isolated in good yields and enantiomeric excess for the reaction promoted by squaramide **10**, or with very moderate enantioselectivity when supported squaramide **8** was used as catalysts (entries 3, 4 in Table 6). Product **20ib** could be formed by a retroaldol reaction in the intermediate hemiacetal, and it has been previously observed in related reactions.[17]

The electronic nature of additional substituents in the phenol derivative does not play significant influence in the reaction. Both 4-bromo-substitued (**13j**) and 4-methyl-2-

(2-nitrovinyl) phenol (**13k**) gave chromenes **19ja** and **19ka**, respectively, in very good yields and excellent enantioselectivities (entries 9-12 in Table 6).

The cyclic pronucleophile derived from cyclopentanone behaves in a similar way than acyclic ones (Scheme 5). The reaction of 2-methoxycarbonyl cyclopentanone (**16f**) with **13i** catalyzed by unsupported squaramide (**10**) occurred very easily leading to a mixture of Michael adduct **21** and hemiacetal **22**. When the mixture was heated with catalytic amount of PTSA (Method A) no dehydration product was formed, and spirochromanone **23if**, resulting from the lactonization of the Michael adduct, was isolated in good yield as a single stereoisomer (entry 1 in Table 7). In contrast, cyclopenta[b]chromene **24if** was obtained in moderate yield and total enantioselection by treatment the mixture with $P_2O_5$ at – 20 $^oC$[16a] (Method B) (entry 2 in Table 7). Total stereoselection, yet lower yield and longer reaction time was observed for the reaction catalyzed by supported squaramide **8** (entry 3), but the reaction time was shortened, maintaining the stereoselection, when the Michael addition was carried out at 50 $^oC$ (entry 4 in Table 7).




**Scheme 5**. Michael addition of methyl 2-oxocyclopentyl carboxylate to 2-(2-nitrovinyl) phenol promoted by **8** and **10**.

**Table 7**. One pot synthesis of chromane derivatives.

| Entry | Catal. | Nucleophile | t (h)[b] | Method | Product (Yield)[c] | Dr[d] | Er[e] |
|---|---|---|---|---|---|---|---|
| 1 | **10** | **16f** | 1 | **A** | **23if** (70) | >98:<2 | >99:<1 |
| 2 | **10** | **16f** | 1 | **B** | **24if** (64) | >98:<2 | >99:<1 |
| 3 | **8** | **16f** | 96 | **B** | **24if** (54) | >98:<2 | 99:1 |
| 4[f] | **8** | **16f** | 6 | **B** | **24if** (50) | >98:<2 | 99:1 |

[a] The reactions were carried out at 0.3 mmol scale with 2 fold excess of nucleophile at rt. [b] Reaction times refer to the Michael addition step. [c] Numbers in parenthesis correspond to isolated products after flash chromatography. [d] Determined by $^1$HNMR, and the given values mean that only a single diastereoisomer was detected. [e] Determined by chiral HPLC. [f] Michael addition-hemiacetalization performed at 50 ºC.

## Conclusions

In summary, we have prepared in two steps novel supported and unsupported bifunctional chiral squaramides from diamines derived from natural amino acids and commercially available alkylamino polystyrenes. Both the homogeneous catalysts and the supported materials are able to catalyze stereoselective Michael additions of different nucleophiles to nitrostyrene derivatives with very good yields and excellent diastereo- and enantioselection. Additionally, the reactions were carried out at rt without solvent, and we have demonstrated that the supported most active catalyst is easily recoverable and reusable for six cycles. Starting from 2-(2-nitrovinyl) phenol as electrophile, a series of some 4*H*-chromenes, and spirochromanes have been prepared, in one pot, with good yields and total stereoselection by hemiacetalization-dehydration or lactonization of the Michael intermediates.

## Experimental

### *General*

$^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) spectra were recorded in $CDCl_3$ or DMSO-$d_6$ as solvent. Chemical shifts for protons are reported in ppm from TMS with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t =

triplet, q = quartet, m = multiplet, br = broad), coupling constants in Hertz, and integration. Specific rotations were measured on a digital polarimeter using a 5-mL cell with a 1-dm path length, and a sodium lamp, and concentration is given in g per 100 mL. FT–IR data are reported in frequency of absorption (only the structurally most important peaks are given). Melting points were obtained with open capillary tubes and are uncorrected. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed on glass-backed plates coated with silica gel 60 and an $F_{254}$ indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed using different chiral columns. Elemental analyses were carried out at the Elemental Analysis Center of the Complutense University of Madrid. HRMS were measured by positive electrospray ionization using quadrupole-time-of-flight detector instrument.

Commercially available organic and inorganic compounds were used without further purification. Solvents were dried and stored over microwave–activated 4 Å molecular sieves. Aminomethyl polystyrene resin (particle size: 160-200 μm, loading: 1.11 mmol/g.), aminoethyl polystyrene resin (particle size: 160-200 μm, loading: 1.05 mmol/g.) and 4-Aminobutyl polystyrene (particle size: 160-200 μm, loading: 1.01 mmol/g.) are commercially available.

Diamines **1-2,**[13] supported thioureas **11-12,**[14] nitroolefins **13c-d,f-g**,[18] and 2-(2-nitrovinyl)phenols **13i-k**,[18] were prepared according to literature procedures**.**

*(S)-3-((1-(Dimethylamino)-3-methylbutan-2-yl)amino)-4-ethoxycyclobut-3-ene-1,2-dione (**3**).* To a solution of 3,4-diethoxy-3-cyclobutane-1,2-dione (0.44 mL, 3 mmol) in DCM (12 mL) was added diamine **1** (0.41 mg, 3.15 mmol) in the same solvent (3 mL). The reaction mixture was stirred at room temperature until complete disappearance of diethyl squarate as monitored by TLC (18 h). The reaction was concentrated in *vacuo* and the residue was purified by flash chromatography (DCM/MeOH: 9:1) to afford **3**: 623 mg (2.45 mmol, 82%). Colorless oil. $[\alpha]_D^{23}$ = +26.4 (c = 1.2, $CHCl_3$). $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 6.8 Hz); 0.92 (d, 3H, J = 7.0 Hz); 1.43 (t, 3H, J = 7.1 Hz); 187 (m, 1H); 2.20 (s, 6H); 2.27 (dd, 1H, J = 12.9, 4.2 Hz); 2.49 (dd, 1H, J = 12.9, 9.9 Hz); 3.59 (m, 1H); 4.77 (q, 2H, J = 7.1 Hz); 6.73 (br s, 1H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 15.8, 17.1, 18.9, 31.4, 45.7, 58.6,

61.1, 69.6, 172.8, 176.6, 182.6, 189.7. IR (ATR): 3481; 3224, 2943, 1802, 1702, 1591, 1426, 1341, 1138, 1026, 865, 827, 730 $cm^{-1}$; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{23}N_2O_3$ 255.1703; Found 255.1704.

*(S)-3-((1-(Dimethylamino)-3,3-dimethylbutan-2-yl)amino)-4-ethoxy cyclobut-3-ene-1,2-dione (**4**).* This compound was obtained from diamine **2** (454 mg, 3.15 mmol) by reaction with 3,4-diethoxy-3-cyclobutane-1,2-dione (0.44 mL, 3 mmol, 0.95 equiv) in DCM as described for **3** and purified by flash chromatography (DCM/MeOH: 9:1) to afford **4**: 761 mg (2.83 mmol, 94%). Colorless oil. $[\alpha]_D^{23}$ = +18.9 (c = 1.1, $CHCl_3$). $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.93 (s, 9H), 1.45 (t, J = 7.1 Hz, 3H), 2.19 (s, 6H), 2.34 (dd, J = 13.0, 2.9 Hz, 1H), 2.45 (m, 1H), 3.47 (m, 1H), 4.75 (q, J = 7.1 Hz, 2H), 6.23 (br s, 1H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 15.9, 26.2, 34.6, 45.6, 59.4, 62.3, 69.5, 173.1, 176.4, 182.4, 189.7; IR (ATR): 3231, 2962, 1802, 1699, 1595, 1422, 1337, 1107, 1037, 819, 727 $cm^{-1}$; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{25}N_2O_3$ 269.1860; Found 269.1861.

**Preparation of resin 5.** To a suspension of (aminomethyl)polystyrene (368 mg, 0.405 mmol) in anhydrous DCM (2.5 mL) was added a solution of **3** (206 mg, 0.81 mmol, 2 equiv) in DCM (2 mL) at 0 °C under nitrogen atmosphere. The resulting suspension was stirred for 48h at room temperature. The resin was collected by filtration, washed with DCM, and dried under vacuum to give 423 mg of polymer **5** (94% yield). IR (ATR): 3262, 3024, 2928, 1798, 1668, 1587, 1533, 1491, 1453, 1345, 1026, 757, 699 $cm^{-1}$. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 3.79. Found: C, 82.25; H, 7.40; N, 4.05; $f$ = 0.96 mmol $g^{-1}$.

**Preparation of resin 6.** This compound was obtained from (2-aminoethyl) polystyrene (340 mg, 0.35mmol) by reaction with **3** (181 mg, 0.7 mmol, 2 equiv) as described for resin **5** to give 372 mg of polymer **6** (90% yield). IR (ATR): 3235, 2924, 1794, 1688, 1587, 1491, 1453, 1353, 1026, 757, 696 $cm^{-1}$. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 3.62. Found: C, 83.12; H, 7.74; N, 3.60; $f$ = 0.86 mmol $g^{-1}$.

**Preparation of resin 7.** This compound was obtained from (4-aminobutyl) polystyrene (378 mg, 0.38 mmol) by reaction with the squaric ester monoamide **3**

(194 mg, 0.76 mmol, 2 equiv) as described for resin **5** to give 265 mg of polymer **7** (60% yield). IR (ATR): 3250, 3028, 2920, 1791, 1688, 1587, 1533, 1495, 1452, 1361, 1030, 757, 696 $cm^{-1}$. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 3.51. Found: C, 82.14; H, 7.68; N, 3.95; $f$ = 0.94 mmol $g^{-1}$.

**Preparation of resin 8.** This compound was obtained from (2-aminoethyl) polystyrene (438mg, 0.46 mmol) by reaction with the squaric ester monoamide **4** (246 mg, 0.92 mmol, 2 equiv) as described for resin **5** to give 436 mg of polymer **8** (81% yield). IR (ATR): 3259, 3029, 2921, 1797, 1667, 1586, 1532, 1490, 1451, 1352; 1029, 757, 699 $cm^{-1}$. A 100% yield of functionalization was calculated on the basis of nitrogen elemental analysis calcd. (%): N, 3.58. Found: C, 82.93; H, 7.59; N, 3.60; $f$ = 0.86 mmol $g^{-1}$.

*(S)-3-(Benzylamino)-4-((1-(dimethylamino)-3-methylbutan-2-yl)amino) cyclobut-3-ene-1,2-dione (**9**).* To a solution of the squaric ester monoamide **3** (422 mg, 1.66 mmol, 1 equiv) in DCM (30 mL) was added benzylamine (0.2 mL, 1.83 mmol, 1.1 equiv), and the mixture was stirred at room temperature for 18 h. The white precipitate was filtered and washed with DCM to afford essentially pure **9**: 419 mg (1.33 mmol, 80%). Colorless solid, mp 237-240 ºC (decomp.). $[\alpha]_D^{23}$ = + 41.6 (c = 0.5, DMSO). $^1$H-NMR (500 MHz, DMSO-$d_6$) δ 0.80 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 1.78 (m, 1H), 2.11 (s, 6H), 2.19 (dd, J = 12.7, 4.6 Hz, 1H), 2.34 (m, 1H), 4.03 (m, 1H), 4.72 (br s, 2H), 7.18 (br s, 1H), 7.26-7.41 (m, 5H), 7.63 (br s, 1H); $^{13}$C-NMR (126 MHz, DMSO-$d_6$) δ 19.7, 31.1, 45.7, 47.3, 56.7, 61.9, 127.9, 128.1, 129.1, 139.3, 167.5, 168.7, 182.6; IR (ATR): 3193, 2970, 1798, 1649, 1556, 1449, 1349, 1034, 745, 696 $cm^{-1}$; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{18}H_{26}N_3O_2$ 316.202; Found 316.2025.

*(S)-3-(Benzylamino)-4-((1-(dimethylamino)-3,3-dimethylbutan-2-yl)amino) cyclobut-3-ene-1,2-dione (**10**).* This compound was obtained from the squaric ester monoamide **4** (169 mg, 0.63 mmol) by reaction with benzylamine (0.075 mL, 0.69 mmol, 1.1 equiv) as described for **9**. The formed white precipitate was filtered and dried in vacuo to give **10**: 176 mg (0.535 mmol, 85%). Colorless solid, mp 248-250 ºC (decomp.). $[\alpha]_D^{23}$ = +59.6 (c = 0.5, DMSO). $^1$H-NMR (500 MHz, DMSO-$d_6$) δ 0.85 (s, 9H), 2.11 (s, 6H), 2.29 (m, 2H), 3.92 (m, 1H), 4.72 (m, 2H), 7.16-7.41 (m, 6H),

7.57 (br s, 1H); $^{13}$C-NMR (126 MHz, DMSO-$d_6$) δ 26.4, 34.6, 45.7, 47.3, 59.8, 60.1, 127.9, 128.2, 129.2, 139.3, 167.3, 168.9, 182.5, 182.7; IR (ATR): 3166, 2951, 2763, 1798, 1641, 1549, 1453, 1341, 1260, 1042, 746. 696 cm$^{-1}$; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{28}N_3O_2$ 330.2176; Found 330.2179.

**General procedure for the catalytic nitro-Michael reaction.** To a mixture of *trans*-β-nitrostyrene (0.3 mmol) and the catalyst (0.015 mmol, 0.05 equiv), was added the corresponding 1,3-dicarbonyl compound (0.6 mmol, 2 equiv) and the reaction mixture was stirred at rt in wheaton vial until consumption of the starting material (TLC). If the used catalyst was homogeneous, the reaction mixture was directly purified by flash chromatography to afford the Michael product. For the reactions catalyzed by supported materials, the catalyst was filtered off and washed with DCM and MeOH. After removal of the solvent under reduced pressure, the crude mixture was purified by flash chromatography to afford the addition product. The diastereomeric ratio was determined by $^1$HNMR spectroscopy of the purified product, and the enantiomeric excess was determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent. Racemic mixtures of the products were synthesized according to the general procedure, but using 1,4-diazabicyclo[2.2.2]octane (DABCO) (2 mg, 0.015 mmol) as catalyst.

**Recyclability of the supported squaramide catalysts in Nitro Michael reaction.** After each cycle, the catalysts were recovered by filtration and washed with DCM and MeOH. After being dried, the supported catalysts could be reused directly without further purification.

*(S)-3-(2-Nitro-1-phenylethyl)pentane-2,4-dione* ***(15aa)***.[19a] Colorless solid (69 mg, 92% yield), mp 122-123 ºC. (Lit.[19b] mp 124-126 ºC); $[\alpha]_D^{23}$ = +216.2 (c = 1.0, $CHCl_3$, er >99:1). [Lit.[19b] $[\alpha]_D^{23}$ = +196.7 (c = 1, $CHCl_3$, er 94:6)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.92 (s, 3H), 2.27 (s, 3H); 4.22 (m, 1H), 4.35 (d, J = 10.8 Hz, 1H), 4.62 (m, 2H), 7.15-7.17 (m, 2H), 7.22-7.35 (m, 3H); HPLC (Lux-amylose-1, hexane/isopropanol 90:10, λ = 220 nm, 1.0 mL/min): $t_R$ = 12.9 min (major, *S*), 17.4 min (minor, *R*). (er > 99:1).

*(S)-3-(1-(4-Chlorophenyl)-2-nitroethyl)pentane-2,4-dione* ***(15ba)***.[19a] Colorless solid (68 mg, 80% yield), mp 124-125 ºC. (Lit.[20] mp 119-121 ºC); $[\alpha]_D^{23}$ = +181.2 (c = 1.4,

$CHCl_3$, er >99:1). [Lit.[20] $[\alpha]_D^{23}$ = -132.5 (c = 1, $CHCl_3$, er 6:94, (*R*)]. $^1$H NMR (500 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.30 (s, 3H), 4.23 (ddd, J = 10.7, 7.6, 5.0 Hz, 1H), 4.33 (d, 1H, J = 10.7 Hz), 4.59 (dd, J = 12.5 Hz, 5.0 Hz, 1H), 4.62 (dd, J = 12.5, 7.6 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H); HPLC (Lux-amylose-1, hexano/isopropanol 80:20, λ = 210 nm, 1.0 mL/min): $t_R$ = 10.2 min (major, *S*), 24.8 min (minor, *R*). (er 97:3).

*(S)-3-(2-Nitro-1-(4-(trifluoromethyl)phenyl)ethyl)pentane-2,4-dione* ***(15ca)***.[21] Colorless solid (74 mg, 78% yield), mp 138-140 ºC. (Lit.[20] mp 144-146 ºC). $[\alpha]_D^{23}$ = +117.2 (c = 1.2, $CHCl_3$, er 99:1). (Lit.[20] $[\alpha]_D^{23}$ = -78.1 (c = 1.1, $CHCl_3$, 91% ee, (*R*)). $^1$H NMR (500 MHz, $CDCl_3$) δ 1.98 (s, 3H), 2.30 (s, 3H), 4.32 (m, 1H), 4.38 (d, 1H, J = 10.6 Hz), 4.63 (dd, J = 12.9 Hz, 4.7 Hz, 1H), 4.67 (dd, J = 12.9, 8.0 Hz, 1H), 7.33 (d, J = 8.1 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H); HPLC (Chiralcel OD, hexane/isopropanol 95:5, λ = 220 nm, 1.0 mL/min): $t_R$ = 40.6 min (major, *S*), 48.9 min (minor, *R*). (er 99:1).

*(S)-3-(2-Nitro-1-(2-nitrophenyl)ethyl)pentane-2,4-dione* ***(15da)***.[22] Colorless solid (78 mg, 88% yield), mp 104-105 ºC. (Lit.[1] mp 112-114 ºC). $[\alpha]_D^{23}$ = +84.3 (c = 1.4, $CHCl_3$, er 99:1). (Lit.[1] $[\alpha]_D^{23}$ = -123.1 (c = 1, $CHCl_3$, 97% ee, (*R*)). $^1$H NMR (500 MHz, $CDCl_3$) δ 2.12 (s, 3H), 2.29 (s, 3H), 4.65 (d, J = 8.7 Hz, 1H), 4.73 (ddd, J = 8.7 Hz, 7.3 Hz, 3.7 Hz), 4.82 (dd, J = 13.3 Hz, 3.7 Hz, 1H), 4.95 (dd, J = 13.3 Hz, 7.2 Hz, 1H), 7.35 (dd, J = 7.9 Hz, 1.4 Hz, 1H), 7.46 (m, 1H), 7.58 (ddd, J = 15.3 Hz, 7.9 Hz, 1.4 Hz, 1H), 7.90 (dd, J = 8.1 Hz, 1.4 Hz, 1H); HPLC (Lux-amylose 1, hexane/isopropanol 90:10, λ = 210 nm, 1.0 mL/min): $t_R$ = 20.7 min (major, *S*), 22.9 min (minor, *R*). (er 99:1).

*(S)-3-(1-(4-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione* ***(15ea)***.[19a] Colorless solid (72 mg, 86% yield), mp 113-114 ºC. (Lit.[20] mp 116-118 ºC). $[\alpha]_D^{23}$ = +156.3 (c = 0.3, $CHCl_3$, er 98:2). (Lit.[20] $[\alpha]_D^{23}$ = -137.1 (c = 1.1, $CHCl_3$, 88%ee, (*R*)). $^1$H NMR (500 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.29 (s, 3H), 3.77 (s, 3H), 4.19 (ddd, J = 10.9, 7.4, 5.3 Hz, 1H), 4.33 (d, J = 10.9 Hz, 1H), 4.59 (m, 2H), 6.84 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 8.7 Hz, 2H); HPLC (Lux-amylose-1, hexane/isopropanol 80:20, λ = 210 nm, 1.0 mL/min): $t_R$ = 14.9 min (major, *S*), 27.8 min (minor, *R*). (er 99:1).

*(S)-3-(1-Naphthalen-1-yl-2-nitro-ethyl)-pentane-2,4-dione (**15fa**).*[23] Colorless oil (81 mg, 90% yield). $[\alpha]_D^{23}$ = +190.3 (c = 1.2, $CHCl_3$, er 99:1). (Lit.[20] $[\alpha]_D^{23}$ = -182.0 (c = 1.1, $CHCl_3$, 95% ee, (*R*)) .$^1$H NMR (500 MHz, $CDCl_3$) δ 1.87 (s, 3H), 2.33 (s, 3H), 4.71 (d, J = 10.5 Hz, 1H), 4.73 (dd, J = 12.2, 4.8 Hz, 1H), 4.82 (dd, J = 12.2, 6.5 Hz, 1H), 5.21 (m, 1H), 7.27 (d, J = 7.3 Hz, 1H), 7.41 (t, J = 7.7 Hz, 1H); 7.55 (t, J = 7.5 Hz, 1H), 7.64 (m, 1H), 7.81 (d, J = 8.2 Hz, 1H), 7.89 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H); HPLC (Chiralpak AS-H, hexane/isopropanol 80:20, λ = 210nm, 0.8 mL/min): $t_R$ = 13.9 min (major, *S*), 17.1 min (minor, *R*). (er 99:1).

*(S)-3-(1-Naphthalen-2-yl-2-nitro-ethyl)-pentane-2,4-dione (**15ga**).*[19a] Colorless solid (75 mg, 83% yield), mp 138-140 ºC. $[\alpha]_D^{23}$ = +98.0 (c = 0.9, $CHCl_3$, er 95:5).$^1$H NMR (500 MHz, $CDCl_3$) δ 1.95 (s, 3H), 2.32 (s, 3H), 4.42 (ddd, J = 10.7, 8.1, 4.4 Hz, 1H), 4.50 (d, J = 10.7 Hz, 1H), 4.69 (dd, J = 12.5, 4.4 Hz, 1H), 4.75 (dd, J = 12.4, 8.1 Hz, 1H), 7.30 (dd, J = 8.5, 1.9 Hz, 1H), 7.49 (m, 2H), 7.65 (m, 1H), 7.80 (m, 2H), 7.83 (d, J = 8.5 Hz, 1H); HPLC (Lux-amylose-1, hexane/isopropanol 90:10, λ = 210 nm, 1.0 mL/min): $t_R$ = 18.3 min (major, *S*), 23.4 min (minor, *R*). (er 95:5).

*(R)-3-(1-(Furan-2-yl)-2-nitroethyl)pentane-2,4-dione (**15ha**).*[1] Colorless solid (60 mg, 84% yield), mp 100-102 ºC. (Lit.[1] mp 94-95 ºC). $[\alpha]_D^{23}$ = +148.7 (c = 1.0, $CHCl_3$, er 97:3). (Lit.[1] $[\alpha]_D^{23}$ = -162.4 (c = 1, $CHCl_3$, 97% ee, (*S*)). $^1$H NMR (500 MHz, $CDCl_3$) δ 2.05 (s, 3H), 2.23 (s, 3H), 4.31 (m, 1H), 4.36 (d, 1H, J = 9.7 Hz), 4.64 (m, 2H), 6.14 (d, J = 3.3 Hz, 1H), 7.26 (dd, J = 3.3, 1.9 Hz, 1H), 7.32 (dd, J = 1.9, 0.7 Hz, 1H); HPLC (Lux-amylose-1, hexano/isopropanol 90:10, λ = 220 nm, 1.0 mL/min): $t_R$ = 13.2 min (major, *R*), 15.6 min (minor, *R*). (er 96:4).

*(S)-2-(2-Nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione (**15ab**).*[19a] Colorless solid (92 mg, 82% yield), mp 144-146 ºC. $[\alpha]_D^{23}$ = +16.1 (c = 1.6, $CH_2Cl_2$, er 91:9). [Lit.[24] $[\alpha]_D^{23}$ = +21.3 (c = 1, $CH_2Cl_2$, er 99:1)]. $^1$H-NMR (500 MHz, $CDCl_3$,) δ 4.63 (m, 1H), 4.99 (d, J = 6.8 Hz, 2H), 5.83 (d, J = 7.9 Hz, 1H), 7.16-7.24 (m, 5H), 7.34-7.41 (m, 4H), 7.49-7.56 (m, 2H), 7.77-7.79 (m, 2H), 7.85-7.87 (m, 2H); HPLC (Lux-amylose-1, hexane/isopropanol 75:25, λ = 210 nm, 1.0 mL/min): $t_R$ = 11.1 min (major, *S*), 27.4 min (minor, *R*). (er 94:6).

*(S)-2-((S)-2-Nitro-1-phenylethyl)-1-phenylbutane-1,3-dione (**15ac**).*[5,25] Colorless solid (80 mg, 86% yield as a mixture 60:40 of diastereoisomers). $^1$H-NMR (500 MHz,

$CDCl_3$, major diast.): δ 1.93 (s, 3H), 4.53 (ddd, J = 10.0, 8.6, 4.6 Hz, 1H), 4.67 (dd, J = 12.6, 8.5 Hz, 1H), 4.72 (dd, J = 12.6, 4.6 Hz, 1H), 5.17 (d, J = 10.1 Hz, 1H), 7.25-7.35 (m, 5H), 7.51 (m, 2H), 7.64 (m, 1H), 8.03 (m, 2H); $^1$H-NMR (500 MHz, $CDCl_3$, minor diast.): δ 2.22 (s, 3H), 4.43 (ddd, J = 10.1, 8.6, 4.3 Hz, 1H), 4.76 (dd, J = 12.8, 4.3 Hz, 1H), 4.85 (dd, J = 12.8, 8.6 Hz, 1H), 5.19 (d, J = 10.2 Hz, 1H), 7.13-7.21 (m, 5H), 7.43 (m, 2H), 7.57 (m, 1H), 7.81 (m, 2H); HPLC (Lux-amylose-1, hexane/isopropanol 97:3, λ = 210 nm, 1.0 mL/min): $t_R$ (major diast.) = 34.6 min (major, *S,S*), 49.4 min (minor, *R,R*). (er 96:4). $t_R$ (minor diast.) = 31.1 min (major, *R,S*), 44.0 min (minor, *S,R*). (er 95:5).

*3-((S)-2-Nitro-1-phenylethyl)-2,4-dioxopentanedinitrile (**15ad**).*[26a] Yellow oil (30 mg, 47% yield). $[\alpha]_D^{23}$ = -1.5 (c = 0.7, $CHCl_3$, er 60:40). [Lit.[26b] $[\alpha]_D^{23}$ = + 5.4 (c = 0.5, $CHCl_3$, er 90:10, (*R*)]. $^1$H-NMR (500 MHz, $CDCl_3$,): δ 4.08 (m, 1H), 4.44 (d, J = 5.9 Hz, 1H), 4.92 (dd, J = 14.3, 6.0 Hz, H), 4.99 (dd, J = 14.3, 8.1 Hz, 1H), 7.34-7.38 (m, 2H), 7.46-7.50 (m, 3H); HPLC (Chiralcel OD, hexane/isopropanol 50:50, λ = 210 nm, 1.0 mL/min): $t_R$ (minor, *R*) =11.3 min, 42.6 min (major, *S*). (er 52:48).

*Diethyl (S)-2-(2-Nitro-1-phenylethyl)malonate (**15ae**).*[19b] Colorless solid (35 mg, 38% yield), mp 42-43 ºC, (Lit.[19b] mp 41-42 ºC). $[\alpha]_D^{23}$ = +4.8 (c = 1.0, $CHCl_3$, er 83:17). (Lit.[19b] $[\alpha]_D^{23}$ = +6.8 (c = 1.0, $CHCl_3$, 95% ee)). $^1$H-NMR (500 MHz, $CDCl_3$): δ 1.03 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 3.80 (d, J = 9.4 Hz, 1H), 3.99 (q, J = 7.1 Hz, 2H), 4.22 (m, 3H), 4.84 (dd, J = 13.0, 9.0 Hz, 1H), 4.91 (dd, J = 13.0, 5.0 Hz, 1H), 7.20-7.32 (m, 5H); HPLC (Lux-amylose-1, hexane/isopropanol 80:20, λ = 220 nm, 1.0 mL/min): $t_R$ = 10.8 min (minor, *R*), 30.4 min (major, *S*). (er 83:17).

*Dimethyl 2-Chloro-2-((S)-2-nitro-1-phenylethyl)malonate (**15af**).*[13] Colorless solid (71 mg, 75% yield), mp 172-174 ºC. $[\alpha]_D^{23}$ = +1.6 (c = 1.0, $CHCl_3$, er 65:35). (Lit.[13] $[\alpha]_D^{23}$ = +4.6 (c = 0.9, $CHCl_3$, er > 99:1)). $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.60 (s, 3H), 3.85 (s, 3H), 4.64 (dd, J = 10.4, 3.4 Hz, 1H), 5.00 (dd, J = 13.6, 10.4 Hz, 1H), 5.22 ((dd, J = 13.6, 3.4 Hz, 1H), 7.30-7.38 (m, 5H); HPLC (Chiralcel OD, hexane/isopropanol 90:10, λ = 220 nm, 1.0 mL/min): $t_R$ (major, *S*) = 10.3 min, 18.1 min (minor, *R*). (er 65:35).

*(2S,3S)-Ethyl 2-Acetyl-4-nitro-3-phenylbutanoate (**15ag**).*[19] Colorless solid (65 mg, 78% yield). $^1$H-NMR (500 MHz, $CDCl_3$) δ 0.98 (t, J = 7.1 Hz, 1.8H), 1.25 (t, J = 7.1

Hz, 1.2H), 2.03 (s, 1.2H), 2.28 (s, 1.8H), 3.94 (q, J = 7.1 Hz, 1.2H), 4.02 (d, J = 9.7 Hz, 0.4H), 4.10 (d, J = 10.0 Hz, 0.6H), 4.22 (m, 1.8H) 4.73 (m, 1.2H), 4.78 (dd, J = 12.9 Hz, J = 8.9 Hz, 0.4H), 4.83 (dd, J = 12.9 Hz, J = 4.9 Hz, 0.4H), 7.17-7.19 (m, 2H), 7.24-7.30 (m, 3H); HPLC (Lux-amylose-1, hexane/isopropanol 95:5, λ = 220 nm, 1.0 mL/min): $t_R$ (major diast.) = 27.1 min (major, 2*S*,3*S*), 39.4 min (minor, 2*R,3R*). (er 96:4). $t_R$ (minor diast.) = 41.5 min (minor, *2S,3R*), 68.6 min (major, *2R,3S*). (er 94:6).

*(R)-3-Methyl-3-(2-nitro-1-phenylethyl)pentane-2,4-dione (**15ah**).*[11b] Colorless oil (70 mg, 89% yield). $[\alpha]_D^{23}$ = +32.5 (c = 1.0, $CHCl_3$, er 99:1). (Lit.[11b] $[\alpha]_D^{23}$ = +29.0 (c = 1, $CHCl_3$, er 93:7)). $^1$H-NMR (500 MHz, $CDCl_3$,) δ 1.39 (s, 3H), 2.00 (s, 3H), 2.06 (s, 3H), 4.19 (dd, J = 11.0, 3.6 Hz, 1H), 4.75 (dd, J = 13.4, 3.6 Hz, 1H), 4.85 (dd, J = 13.4, 11.0 Hz, 1H), 7.14-7.16 (m, 2H), 7.24-7.30 (m, 3H); HPLC (Lux-amylose-1, hexane/isopropanol 95:5, λ = 210 nm, 1.0 mL/min): $t_R$ = 17.1 min (minor, *S*), 20.1 min (major, *R*). (er 99:1).

*(2R,3R)-Ethyl 2-Acetyl-2-methyl-4-nitro-3-phenylbutanoate (**15ai**).*[27] Colorless solid (65 mg, 74% yield). $^1$H-NMR (500 MHz, $CDCl_3$, major diast.) δ 1.18 (t, *J* = 7.2 Hz, 1.8H), 1.22 (s, 1.2H), 1.29 (t, *J* = 7.1 Hz, 1.2H), 1.42 (s, 1.8H), 2.10 (s, 1.8H), 2.15 (s, 1.2H), 3.98–4.15 (m, 1.6H), 4.22 (m, 0.6H), 4.26 (q, J = 7.1 Hz, 0.8H), 4.86–4.98 (m, 2H), 7.11–7.13 (m, 0.8H), 7.19–7.22 (m, 1.2H), 7.25–7.30 (m, 3H); HPLC (Chiralcel OD, *n*-hexane/2-propanol = 98/2, 1 mL/min, λ = 220 nm): $t_R$ (major diastereoisomer) = 16.1 min (major, 2*R*,3*R*), 24.6 min (minor, 2*S*,3*S*); $t_R$ (minor diastereoisomer) = 14.3 min (major, 2*S*,3*R*), 34.5 min (minor, 2*R*,3*S*).

*(S)-Ethyl 1-((R)-2-Nitro-1-phenylethyl)-2-oxocyclopentanecarboxylate (**17aa**).*[27] Colorless oil (78 mg, 85% yield). $[\alpha]_D^{23}$ = +32.8 (c = 1.0, $CHCl_3$, er >99:1). (Lit.[27] $[\alpha]_D^{23}$ = +30.8 (c = 1, $CHCl_3$, er 96:4)). $^1$H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 1.81-2.06 (m, 4H), 2.36 (m, 2H), 4.07 (dd, J = 10.9, 3.8 Hz, 1H), 4.21 (m, 2H), 5.01 (dd, J = 13.6, 11.0 Hz, 1H), 5.17 (dd, J = 13.6, 3.8 Hz, 1H), 7.25-7.32 (m, 5H); HPLC (Chiralcel OD, hexane/isopropanol 80:20, λ = 220 nm, 1.0 mL/min,): $t_R$ (major diast.) = 8.1 min (major, *S,R*), 11.1 min (minor, *R,S*). (er > 99:1).

*(S)-Ethyl 1-((R)-2-Nitro-1-phenylethyl)-2-oxocyclohexanecarboxylate (**17ab**).*[27] Colorless solid (79 mg, 82% yield). mp 101-103 ºC. $[\alpha]_D^{23}$ = -88.2 (c = 1.0, $CHCl_3$, er 98:2). (Lit.[27] $[\alpha]_D^{23}$ = -86.5 (c = 1, $CHCl_3$, er 97:3)). $^1$H NMR (500 MHz, $CDCl_3$) δ

1.24 (t, J = 7.1 Hz, 3H), 1.42-1.73 (m, 4H), 2.05 (m, 2H), 2.45 (m, 2H), 3.98 (dd, J = 11.2, 3.2 Hz, 1H), 4.19 (m, 2H), 4.78 (dd, J = 13.4, 11.2 Hz, 1H), 5.04 (dd, J = 13.4, 3.2 Hz, 1H), 7.13 (m, 2H), 7.25 (m, 3H); HPLC (Chiralcel OD, hexane/isopropanol 95:5, λ = 220 nm, 1.0 mL/min): $t_R$ (major diast.) = 10.5 min (major, *S,R*), 14.9 min (minor, *R,S*). (er 98:2).

*(S)-Methyl 1-((R)-2-Nitro-1-phenylethyl)-2-oxocycloheptanecarboxylate* ***(17ac)***.[27] Colorless oil (98 mg, 98% yield). $[\alpha]_D^{23}$ = -27.3 (c = 0.8, $CHCl_3$, er >99:1). $^1$H-NMR (500 MHz, $CDCl_3$,): δ 1.42 (m, 1H); 1.52-1.61 (m, 4H), 1.67 (m, 1H); 1.76 (m, 1H); 1.90 (m, 1H); 2.51 (m, 1H), 2.61 (m, 1H), 3.77 (s, 3H), 4.06 (dd, J = 10.1, 4.1 Hz, 1H), 4.92 (dd, J = 13.6, 10.1 Hz, 1H), 4.96 (dd, J = 13.6, 4.1 Hz, 1H), 7.13-7.16 (m, 2H), 7.27-7.32 (m, 3H); HPLC (Chiralcel OD, hexane/isopropanol 95:5, λ = 220 nm, 1.0 mL/min): $t_R$ (major diast.) = 12.9 min (major, *S,R*). (er 100:0).

*(R)-2-Acetyl-2-((R)-2-nitro-1-phenylethyl)cyclopentanone* ***(17ad)***.[27] Colorless solid (78 mg, 94% yield, as a mixture of *anti/syn* (81: 19) diastereoisomers). $^1$H-NMR (500 MHz, $CDCl_3$, major diast.): δ 1.68-1.76 (m, 3H), 1.97 (m, 1H), 2.19 (m, 1H), 2.33 (s, 3H), 2.57 (m, 1H), 4.39 (dd, J = 11.5, 3.9 Hz, 1H), 4.51 (dd, J = 13.5, 3.9 Hz, 1H), 4.86 (dd, J = 13.5, 11.5 Hz, 1H), 7.24-7.33 (m, 5H); HPLC (Chiralcel OD, hexane/isopropanol 70:30, λ = 220 nm, 1.0 mL/min): $t_R$ (major diast.) = 10.6 min (major, *R,R*), 43.4 min (minor, *S,S*). (er 100:0). $t_R$ (minor diast.) = 12.6 min (major, *S,R*), 18.6 min (minor, *R,S*). (er 100:0).

*(R)-3-Acetyl-dihydro-3-((R)-2-nitro-1-phenylethyl)furan-2(3H)-one* ***(17ae)***.[27] Colorless solid (66 mg, 80% yield, as a mixture of *anti/syn* (56: 44) diastereoisomers). $^1$H-NMR (500 MHz, $CDCl_3$, major diast.): δ 2.25-2.35 (m, 1H) 2.49 (s, 3H), 2.84 (m, 1H), 3.85 (td, J = 8.9, 4.2 Hz, 1H), 4.03 (dt, J = 8.9, 7.8 Hz, 1H), 4.49-4.56 (m, 2H), 4.85 (dd, J = 13.1, 10.9 Hz, 1H), 7.33-7.37 (m, 5H); $^1$H-NMR (500 MHz, $CDCl_3$, minor diast.): δ 2.22-2.31 (m, 1H), 2.34 (s, 3H), 2.57 (m, 1H), 3.85 (td, J = 8.9, 4.2 Hz, 1H), 4.09 (td, *J* = 8.9, 5.6 Hz, 1H), 4.34 (dd, J = 11.2, 3.6 Hz, 1H), 4.74 (m, J = 13.4, 3.6 Hz, 1H), 5.06 (dd, J = 13.4, 11.2 Hz, 1H), 7.28-7.32 (m, 2H), 7.33-7.39 (m, 3H); HPLC (Chiralcel OD, hexane/isopropanol 70:30, λ = 220 nm, 1.0 mL/min): $t_R$ (major diast.) = 10.6 min (major, *R,R*). (er 100:0). $t_R$ (minor diast.) = 12.8 min (major, *S,R*), 20.9 min (minor, *R,S*). (er 97:3).

**General procedure for One-Pot synthesis of 19 and 23.** To a mixture of *(E)*-2-(2-nitrovinyl)phenol (0.3 mmol) and catalyst (0.015 mmol, 0.05 equiv), 1,3-dicarbonyl compound (0.6 mmol, 2 equiv) was added and the reaction mixture was stirred at rt in wheaton vial until consumption of the starting material (TLC). In the reactions catalyzed by homogeneous catalyst **10**, toluene (5 mL per mmol) and PTSA monohydrate (20 mol%) were added, and the mixture was heated for 2h at 100 $^{o}$C. The solution was cooled to rt, the solvent eliminated under vacuum, and the residue was purified by flash chromatography to afford the product. The same experimental procedure was followed for the reactions catalyzed by supported squaramide **8**, except that the catalyst was separated by filtration before treatment with Toluene/PTSA. The enantiomeric excess was determined by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

*(S)-1-(2-Methyl-4-(nitromethyl)-4H-chromen-3-yl)ethan-1-one* ***(19ia)***. This compound was purified by column chromatography on silica gel (eluent: hexane/EtOAc 8/1): 69 mg (93% yield). Colorless oil. $[\alpha]_D^{23}$ = -23.7 (c = 0.5, $CHCl_3$) (er 99:1). $^1$H-NMR (500 MHz, $CDCl_3$) δ 2.46 (s, 3H), 2.47 (s, 3H), 4.37 (dd, J = 11.6, 8.0 Hz, 1H), 4.49 (dd, J = 11.6, 4.2 Hz, 1H), 4.65 (dd, J = 8.0, 4.2 Hz, 1H), 7.06 (d, J = 8.1Hz, 1H), 7.09-7.15 (m, 1H), 7.18 (dd, J = 7.6, 1.8 Hz), 7.24-7.32 (m, 1H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 20.9, 30.9, 35.1, 80.2, 111.4, 116.3, 120.6, 125.2, 128.1, 128.9, 150.5, 163.7, 196.7; IR (ATR): 2919, 1680, 1629, 1582, 1543, 1487, 1460, 1377, 1357, 1227, 1188, 943, 758 cm$^{-1}$; HRMS (ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{13}H_{14}NO_4$ 248.0917; Found 248.0921; HPLC (Chiralcel OD, hexane/isopropanol 90:10, λ = 254 nm, 1.0 mL/min): $t_R$ =14.2 min (major, *S*), 18.0 min (minor, *R*).

*(S)-1-(2-Ethyl-4-(Nitromethyl)-4H-chromen-3-yl)propan-1-one* ***(19ij)***. This compound was purified by column chromatography on silica gel (eluent: hexane/EtOAc 15/1): 69 mg (84% yield). Colorless oil. $[\alpha]_D^{23}$ = -36.6 (c = 1.2, $CHCl_3$) (er 99:1). $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.16 (t, J = 7.2 Hz, 3H), 1.26 (t, J = 7.5 Hz, 3H); 2.74 (m, 4H), 4.31 (dd, J = 11.7, 8.5 Hz, 1H), 4.48 (dd, J = 11.7, 4.4 Hz, 1H), 4.63 (dd, J = 8.5, 4.4 Hz, 1H), 7.05-7.10 (m, 1H), 7.12 (dd, J = 7.4, 1.0 Hz, 1H), 7.16 (dd, J = 7.6, 1.7 Hz, 1H), 7.24-7.32 (m, 1H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 8.7, 11.7, 26.6, 35.0, 35.5, 80.2, 110.1, 116.2, 120.8, 125.0, 128.0, 128.9, 150.8, 166.9, 200.3; IR (ATR): 2978, 2935, 1684, 1629, 1582, 1546, 1487, 1460, 1377, 1361, 1227, 1188, 919, 758 cm$^{-1}$; HRMS

(ESI-QTOF) m/z: $[M + H]^+$ Calcd for $C_{15}H_{18}NO_4$ 276.1230; Found 276.1233; HPLC (Chiralcel OD, hexane/isopropanol: 98:2, λ = 254 nm, 1 mL/min): $t_R$ = 11.0 min (major, *S*), 24.5 min (minor, *R*).

*(S)-Methyl 2-Methyl-4-(nitromethyl)-4H-chromene-3-carboxylate* ***(19ik)***.[16b] This compound was purified by column chromatography on silica gel (eluent: hexane/EtOAc 8/1): 57 mg (72% yield). Colorless solid. mp 91-92 ºC. (Lit.[16b] mp 93 ºC). $[\alpha]_D^{23}$ = -64.0 (c = 0.5, $CHCl_3$). (er >99:<1). [Lit.[16b] $[\alpha]_D^{23}$ = +88.4 (c = 1.0, $CHCl_3$, 98% ee) for (*R*) enantiomer]. $^1$H-NMR (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 3.82 (s, 3H), 4.41 (dd, J = 11.6, 7.8 Hz, 1H), 4.56 (dd, J = 11.6, 4.4 Hz, 1H), 4.65 (dd, J = 7.8, 4.4 Hz, 1H), 7.04 (dd, J = 8.2, 1.2 Hz, 1H), 7.12 (td, J = 7.4, 1.2 Hz, 1H), 7.17 (dd, J = 7.7, 1.9 Hz, 1H), 7.24-7.32 (m, 1H); HPLC (Chiralpak IA, hexane/isopropanol 95:5, λ = 254 nm, 0.5 mL/min): $t_R$ = 16.1 min (major, *S*), 16.8 min (minor, *R*).

*(S)-1-(6-Bromo-2-methyl-4-(nitromethyl)-4H-chromen-3-yl)ethanone* ***(19ja)***. This compound was purified by column chromatography on silica gel (eluent: hexane/EtOAc 4/1): 80 mg (82% yield). Colorless oil. $[\alpha]_D^{23}$ = +53.4 (c = 0.8, $CHCl_3$) (er 99:1). $^1$H-NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.45 (s, 3H), 4.40 (dd, J = 12.0, 7.4 Hz, 1H), 4.46 (dd, J = 12.0, 4.2 Hz, 1H), 4.58 (dd, J = 7.4, 4.2 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.37 (dd, J = 8.6, 2.4 Hz); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 20.9, 31.0, 34.8, 79.9, 111.2, 117.5, 118.1, 122.8, 130.7, 132.0, 149.7, 163.5, 196.5; IR (ATR): 2923, 1680, 1625, 1546, 1479, 1377, 1231, 1184, 817, 730 $cm^{-1}$; HRMS (ESI-QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{12}BrNO_4Na$ 347.9842; Found 347.9856; HPLC (Chiralcel OD, hexane/isopropanol 90:10, λ = 254 nm, 1.0 mL/min): $t_R$ = 18.7 min (major, *S*), 22.6 min (minor, *R*).

*(S)-1-(2,6-Dimethyl-4-(nitromethyl)-4H-chromen-3-yl)ethanone* ***(19ka)***. This compound was purified by column chromatography on silica gel (eluent: hexane/EtOAc 4/1): 60 mg (77% yield). Colorless oil. $[\alpha]_D^{23}$ = +14.0 (c = 0.8, $CHCl_3$) (er >99:<1). $^1$H-NMR (500 MHz, $CDCl_3$): δ 2.15 (s, 3H), 2.44 (s, 3H), 2.45 (s, 3H), 4.40 (dd, J = 12.0, 7.5 Hz, 1H), 4.46 (dd, J = 12.0, 4.2 Hz, 1H), 4.58 (dd, J = 7.5, 4.2 Hz, 1H), 6.93 (d, J = 8.6 Hz, 1H); 7.32 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.6, 2.3 Hz, 1H); $^{13}$C-NMR (126 MHz, $CDCl_3$) δ 20.8, 21.0, 30.9, 35.2, 80.2, 111.2, 116.0, 120.3, 128.2, 129.6, 134.9, 148.5, 164.0, 196.8; IR (ATR): 2923, 1685, 1625, 1546, 1499, 1424, 1377, 1254, 1211, 947, 817, 734, 671 $cm^{-1}$; HRMS (ESI-QTOF) m/z: $[M + H]^+$

Calcd for $C_{14}H_{16}NO_4$ 262.1074; Found 262.1076; HPLC (Chiralcel OD, hexane/isopropanol 90:10, λ = 254 nm, 1.0 mL/min): $t_R$ = 11.1 min (major, *S*), 14.9 min (minor, *R*).

*(R)-2-(1-Nitro-4-oxopentan-2-yl)phenyl benzoate (**20ib**).*[17a] To a mixture of (*E*)-2-(2-nitrovinyl)phenol (50 mg, 0.3 mmol), and catalyst **10** (5 mg, 0.015 mmol, 0.05 equiv), was added a solution of dibenzoylmethane (135 mg, 0.6 mmol, 2 equiv) in DCM (0.4 mL), and the reaction mixture was stirred at rt in a wheaton vial until consumption of the starting material (TLC). The crude reaction mixture was purified by flash chromatography (hexane/ethyl acetate 4/1) to yield **20ib** (93 mg, 80% yield). Colorless oil. $[\alpha]_D^{23}$ = +7.0 (c = 0.9, $CHCl_3$) (er 93:7). $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.41 (dd, J = 17.6, 7.9 Hz, 1H), 3.49 (dd, J = 17.6, 6.0 Hz, 1H), 4.47 (m, 1H), 4.76 (dd, J = 12.7, 7.4 Hz, 1H), 4.81 (dd, J = 12.7, 6.9 Hz, 1H), 7.24 (m, 2H), 7.37 (m, 3H), 7.52 (m, 2H), 7.65 (m, 1H), 7.85 (d, J = 7.8 Hz, 2H), 8.22 (d, J = 7.7 Hz, 2H); HPLC (Lux-amylose-1, hexane/isopropanol 90:10, λ = 220 nm, 1.0 mL/min): $t_R$ = 25.2 min (major, *S*), 26.8 min (minor, *R*).

*(1'S,4R)-4-(Nitromethyl)spiro[chroman-3,1'-cyclopentane]-2,2'-dione (**23if**).*[16a] This compound was purified by column chromatography on silica gel (eluent: hexane/EtOAc 4/1): 58 mg (70% yield). Colorless solid. mp 157-159 ºC. (Lit.[16a] mp 159 ºC). $[\alpha]_D^{23}$ = -36.0 (c = 0.4, $CHCl_3$) (er >99:<1). [Lit.[16a] $[\alpha]_D^{23}$ = -42.4 (c = 1.0, $CHCl_3$, 99% ee) for (1'*S*,4*R*) stereoisomer]. $^1$H-NMR (500 MHz, $CDCl_3$) δ 1.93-2.10 (m, 3H), 2.18 (m, 1H), 2.47 (m, 1H), 2.68 (m, 1H), 3.78 (dd, J = 10.1, 5.0 Hz, 1H), 4.40 (dd, J = 13.5, 10.1 Hz, 1H), 5.54 (dd, J = 13.5, 5.0 Hz, 1H), 7.00-7.20 (m, 3H), 7.38 (ddd, J = 8.2, 7.0, 2.0 Hz, 1H); HPLC (Chiralcel OD, hexane/isopropanol 90:10, λ = 220 nm, 1 mL/min): $t_R$ = 35.2 min (major), 46.2 min (minor).

*Methyl (9R,9aS)-9-(Nitromethyl)-1,2,9,9a-tetrahydrocyclopenta [b]chromene-9a-carboxylate (**24if**).*[16a] To a mixture of *(E)*-2-(2-nitrovinyl)phenol (50 mg, 0.3 mmol) and catalyst **10** (5 mg, 0.015 mmol, 0.05 equiv), was added methyl 2-oxocyclopentanecarboxylate (0.075 mL, 0.6 mmol, 2 equiv) and the reaction mixture was stirred at rt in a wheaton vial and monitored by TLC. After complete conversion of the starting material, DCM (1.8 mL) and $P_2O_5$ (128 mg, 0.9 mmol, 3 equiv) were added and stirred for 2d at -20 ºC. The crude reaction mixture was then filtered through a small pad of silica gel and purified by flash chromatography (DCM/pentane:

1/2) to yield **24if** (55 mg, 64% yield). Colorless solid, mp 155-156 ºC. (Lit.[16a] mp 158 ºC). $[\alpha]_D^{23}$ = -76.0 (c = 0.3, $CHCl_3$) (er >99:1). (Lit.[16a] $[\alpha]_D^{23}$ = -85.0 (c = 1.0, $CHCl_3$) for (9*R*,9a*S*) stereoisomer). $^1$H-NMR (500 MHz, $CDCl_3$): 2.02-2.11 (m, 1H), 2.25-2-39 (m, 2H), 2.44 (dddd, J = 15.4, 8.8, 6.7, 2.1 Hz, 1H), 3.54 (s, 3H), 4.24 (dd, J = 12.5, 8.4 Hz, 1H), 4.31 (dd, J = 8.4, 5.8 Hz, 1H), 4.66 (dd, J = 12.5, 5.8 Hz, 1H), 5.37 (dd, J = 2.8, 2.2 Hz, 1H), 6.89-6.96 (m, 2H), 7.07 (ddd, J = 8.1, 1.7, 0.6 Hz, 1H), 7.21 (ddd, 8.3, 7.5, 1.7 Hz, 1H); HPLC (Chiralpak IA, hexane/isopropanol 90:10, λ = 254 nm, 1 mL/min): $t_R$ = 8.6 min (major, *R*), 9.1 min (minor, *S*).

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**Supporting Information Available**: Copies of $^1$H-NMR and $^{13}$C-NMR spectra for all new compounds, IR (ATR) for supported squaramides, and copies of the HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org

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