Catalysis Science & Technology

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/catalysis

Journal Name

COMMUNICATION

Removing the superfluous: a supported squaramide catalyst with a minimalistic linker applied to the enantioselective flow synthesis of pyranonaphthoquinones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Laura Osorio-Planes,[a] Carles Rodríguez-Escrich [a] and Miquel A. Pericàs *[,a,b]

A continuous flow setup has been implemented for the enantioselective production of a library of pyranonaphthoquinones. This was possible through a sequential two-step process involving a squaramide-catalyzed Michael reaction and an oxa-Michael cyclization. A key factor for the success of this methodology was the development of a new, cost-effective polystyrene-supported squaramide.

The incorporation of flow techniques as new processing tools is slowly reshaping the way the chemical community tackles synthetic problems. Compared to the traditional batch vessels, continuous flow reactors have significant advantages such as enhanced heat and mass transfer and optimum mixing, which allow for a quick and precise adjustment of reaction parameters. Moreover, at industrial scale, benefits include enhanced safety, direct scale-up and reduced downstream processing costs and efforts.[1]

To embrace the construction of chiral molecules with high added value, asymmetric catalysts have to be incorporated in the continuous flow setup. In this regard, a packed-bed column filled with a heterogenized catalyst resembles the ideal scenario since catalyst separation, recovery and reuse are achieved in one single operation, thus minimizing the downstream processing costs. Moreover, due to the pseudo-overstoichiometric catalyst/substrate instant conditions –which shorten reaction times– and the continuous outflow of products, overreactions are minimized, thus increasing selectivity. Additionally, no stirring is required in flow operation, which suppresses mechanical degradation issues and leads to increased lifetimes of the immobilized catalyst. Consequently, considerable attention has been addressed towards this field over the past few years, with special focus in the immobilization of chiral organocatalysts onto solid supports such as polystyrene and their application in a flow stream.[2] Despite all these inherent advantages of heterogenized catalysts, the field is still far from being fully exploited. The main reason for this lies on the fact that covalent immobilization often implies multistep functionalization sequences that can hamper their cost-effectiveness. With the aim of minimizing synthetic economical costs and effort as well as expanding their applicability to industry, research focused on the rational design of the connection between catalyst and support is crucial.

Recently, our group reported a very efficient and enantioselective polystyrene-supported (PS) squaramide **1** (Figure 1) that was first applied in batch[3] and later in flow for the Michael addition of 2-hydroxy-1,4-naphthoquinone to nitrostyrenes.[4]

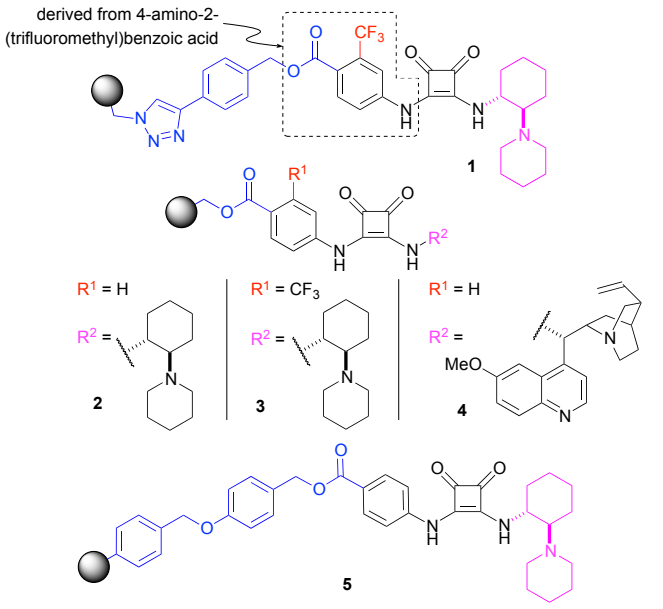


Figure 1 PS-supported squaramides evaluated in this work.

[a] *Institute of Chemical Research of Catalonia (ICIQ), The Barcelona Institute of Science and Technology*
Av. Països Catalans, 16, 43007 Tarragona (Spain)
E-mail: mapericas@iciq.es
[b] *Departament de Química Orgànica*
Universitat de Barcelona, 08080 Barcelona (Spain)
Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x

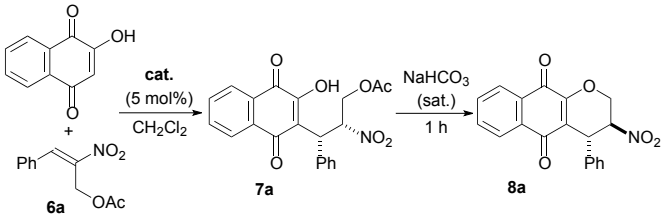
Although the synthesis of this heterogenized catalyst was rather straightforward (5 steps) we identified two possible "weak spots" that could hinder its applicability towards other systems. The first one was the presence of the triazole moiety: we have observed that in some instances it can interfere in the reaction course due to its moderate basic and nucleophilic nature.[2d, 5] An additional issue was the use of 4-amino-2-(trifluoromethyl)benzoic acid, a highly expensive building block that substantially raised the total cost of the catalyst. Therefore, in the present work we pursued to study whether these two scaffolds could be eluded without sacrificing the previous catalytic performance.

Recently, Namboothiri and da Silva Jr. have reported the use of a chiral quinine-derived squaramide in the synthesis of highly enantioenriched pyranones and pyranonaphthoquinones.[6] We found this transformation to be very appealing to develop our investigation since it gives access to structures with pronounced biological and pharmacological properties. To name a few, pyranonaphthoquinones are known to display anticancer,[7] antileishmanial,[7c, d, 8] and antibacterial activity.[7d, 9] Thus, we started our studies testing PS-squaramide **1** in the addition of 2-hydroxy-1,4-naphthoquinone to (*E*)-2-nitro-3-phenylallyl acetate **6a** (Table 1). We were delighted to observe that this specific catalyst was highly active and enantioselective for the Michael reaction, rendering the product in only 2 h and 98% ee (Table 1, entry 1). However, with supported squaramide **1** the reaction stopped at intermediate **7a**, whereas the subsequent oxa-Michael addition to afford the desired pyranonaphthoquinone **8a** was only achieved after one hour of basic treatment with sodium bicarbonate.[†] In spite of this, the stereochemical outcome was completely maintained. Next, we moved to evaluate the effect of the $-CF_3$ group in the aromatic moiety of the organocatalyst. To this aim, three different PS-squaramides (Figure 1, **2**-**4**) were prepared in a very convenient 3-step sequence, starting from commercially available compounds.[‡]

In this regard, unappreciable difference in catalytic performance was observed between catalysts **2** and **3**, varying only in the presence of the trifluoromethyl group (Table 1, entries 2 and 3). Additionally, for the sake of comparison with the reported homogeneous procedure,[6a] the corresponding PS-quinine derivative **4** was also tested (Table 1, entry 4). However, in all these cases the reaction turned out to be slower than with our initial catalyst **1**.

After a positive influence of the electron-withdrawing CF_3 group had been ruled out, we turned our sights onto the length of the linker as the possible responsible for such a difference in reactivity. Consequently, a new PS-squaramide **5** was prepared following an alternative approach that allowed to install a longer spacer without introducing additional synthetic steps (Scheme 1). The previously used Merrifield resin was replaced by the Wang resin, which already contains a bis-phenylmethylene ether handle. The intermediate **9** was then immobilized using a typical peptide coupling procedure (perfectly suited for work with polystyrene resins) and the final bifunctional catalyst was achieved after nucleophilic displacement with the chiral amine **11**.

Table 1 Screening of catalysts.[a]

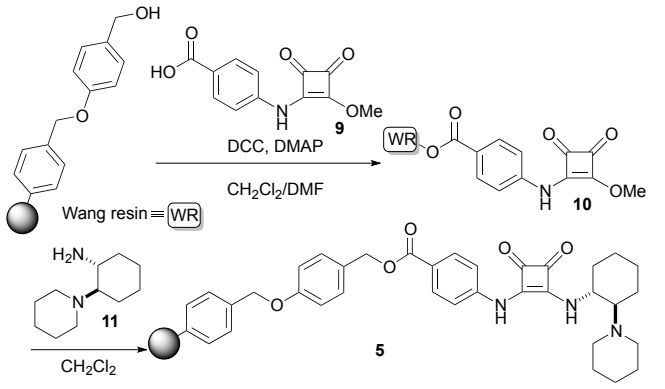


Entry	Cat.	Time (h)	Yield (%)	dr	ee (%)
1	**1**	2	64	94:6	98
2	**2**	7	76	90:10	96
3	**3**	6	75	90:10	96
4	**4**	8	61	92:8	–95
5	**5**	1	87	>95:5	98

[a]Reaction conditions: **6a** (0.060 mmol), 2-hydroxy-1,4-naphthoquinone (0.070 mmol) and 3.2 µmol of catalyst in 0.25 mL of CH_2Cl_2. Then, the resin was filtered, 0.5 mL $NaHCO_3$ (sat) were added and it was stirred for a further one hour.

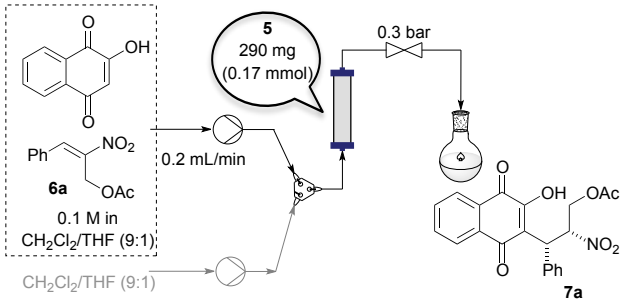
Very gratifyingly, when this new resin **5** was applied in the benchmark reaction, optimal results were obtained: there was a 50% reduction in reaction time in comparison with PS-squaramide **1** (from 2 to 1 h) and the enantioselectivity was maintained as high as 98%[§] (Table 1, entry 5). Once the best catalyst was identified, other solvents were also evaluated.[‡] Even though our initial choice (CH_2Cl_2) resulted to be the best partner for this system, greener solvents like EtOAc also rendered the product with excellent ee's (97%) in a slightly longer reaction time (3 h).

With the optimized reaction conditions in hand, the continuous flow experiment was addressed. Since the target transformation is actually comprised of two sequential reactions –the organocatalyzed Michael addition and the base-promoted cyclization– the two processes were first investigated independently. With respect to the enantioselective reaction, the experimental setup consisted of a packed bed reactor (¼" Teflon tube) loaded with PS-squaramide **5** (Table 2). Conveniently, due to the negligible background reaction in the absence of catalyst, the starting materials could be mixed in a single feed solution.



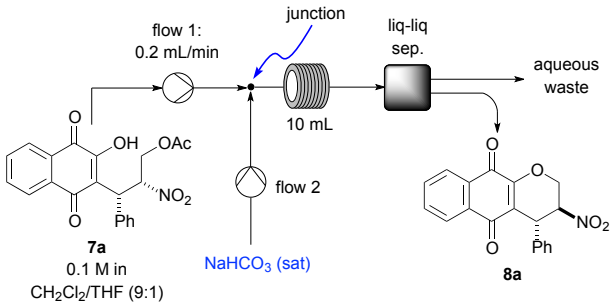
Scheme 1 Synthesis of PS-squaramide **5**.

Table 2 Enantioselective Michael addition under flow conditions.



Entry	t (h)	Conv. (%)	ee (%)
1	0.5	97	97
2	1.5	97	97
3	3	96	98
4	4	97	98

Table 3 Optimization of reaction parameters of the cyclization reaction in flow.



Entry	Junction	Flow 2 (mL/min)	Conv. (%)
1	Y-junction	0.2	54
2	Y-junction	0.3	69
3	T-junction	0.3	89
4	T-junction	0.45	100

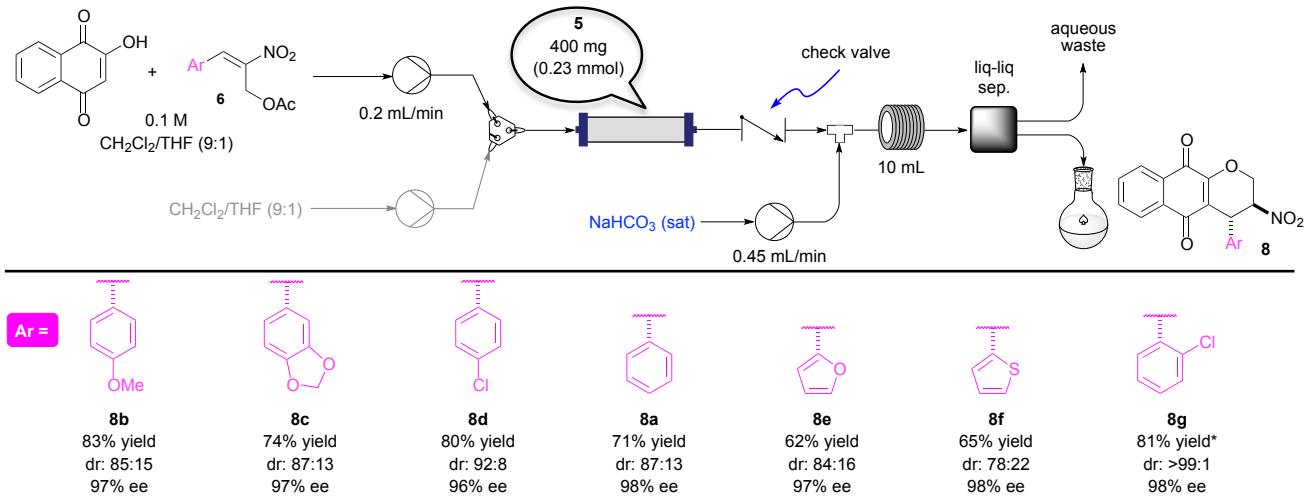
Upstream, the column was connected with a Y-junction to two channels, one containing the reagents solution and the other one with solvent. Thus, the heterogenized catalyst could be alternatively fed with the starting materials or swollen/rinsed with the solvent. Downstream, a back-pressure regulator was incorporated to prevent bubble formation due to the volatility of CH_2Cl_2. To perform this experiment, 4.5 mmol (1 g) of nitroalkene **6a** were used together with 1.1 equiv. of hydroxynaphthoquinone.[§§] It was demonstrated that a flow rate of 0.2 mL/min was optimal to perform this reaction with the amount of catalyst used (290 mg). The starting solution was consumed after 4 h and both conversion and enantioselectivity remained high during the whole process (Table 2).

Having established the parameters for the first reaction we moved to study the oxa-Michael cyclization in flow with the aim of performing both processes in a sequential manner. The setup for this transformation is depicted in Table 3. The outstream collected in the previous reaction was directly used as the starting solution without any further purification. To this, a second pump with saturated aqueous $NaHCO_3$ solution was connected with a Y-junction and a 10 mL coil (Ø = 0.8 mm, PTFE) was used as a reactor. The biphasic mixture was subsequently separated in-line using a Zaiput liquid-liquid separator. Since the flow rate of the organic phase was already predetermined, the same 0.2 mL/min were initially tested for the aqueous stream; however, the conversion turned out to be rather poor (54%; Table 3, entry 1). Increasing the flow rate of the aqueous phase to 0.3 mL/min was translated into a considerable improvement (69%; Table 3, entry 2). At this stage, it was observed that the segments of the biphasic system in the coil were rather large, pointing out to an inefficient mixture. In view of this, the Y-junction was replaced by a T-junction with a much smaller internal volume. Indeed, the segments became shorter and the conversion raised to 89% (Table 3, entry 3). Finally, full conversion was achieved by increasing the flow rate up to 0.45 mL/min. It should be noted that other bases and buffer solutions were also tested in this system. Nevertheless, they led to slower reactions or formation of by-products.[‡]

Once both reactions were optimized separately, we set our sights into telescoping the whole process. Taking into account the potential biological value of enantioenriched pyranonaphthoquinones, we addressed the preparation of a library of analogues by sequential pumping of different substrate combinations in a flow device. Thus, a new setup was assembled in which the outlet of the column (packed with 400 mg of **5**) was coupled with the T-junction connecting the base solution and the coil reactor (Scheme 2). Since the required flow rate of the base turned out to be considerably higher than that of the starting materials, a check valve was positioned after the column to prevent potential contamination of the chiral resin. Seven solutions containing hydroxynaphthoquinone and a representative set of Morita-Baylis-Hillman acetates **6** (1 mmol each) were prepared. Every combination was pumped through the system and subsequently rinsed with solvent at equal flow rate for 1 h. The same operation was repeated for each solution. Remarkably, the total residence time of the process including the two reactions and in-line work-up was only 30 min. As depicted in Scheme 2, all the pyranonaphthoquinones prepared with this methodology showed excellent stereoselectivities and good yields regardless of the electronic nature of the aryl ring of the nitro olefin (**8a**-**8g**). The absolute configuration of **8e** was assigned by comparison of the optical rotation value with the one reported in the literature,[6a] the rest being assigned by analogy to **8e**.

Conclusions

A new, simple and low-cost immobilized chiral squaramide has been rationally developed to expand the applicability of its predecessors. Indeed, with this study it has been demonstrated that the selection of the proper linker is crucial for the optimal performance of the heterogenized catalytic species. Besides, in this specific case this has allowed to avoid the use of expensive building blocks without any loss of catalytic behaviour. Moreover, this polystyrene-supported resin has been implemented in a continuous flow device for the production of a library of highly enantioenriched



* New resin was used.

Scheme 2 Enantioselective continuous flow production of a library of pyranonaphthoquinones.

pyranonaphthoquinones by means of a sequential two-step synthesis. We believe this work could be of interest in the drug discovery field as it provides easy access to a variety of structures with potential biological activity.

Acknowledgments

This work was funded by the Institute of Chemical Research of Catalonia (ICIQ) Foundation, MINECO (grant CTQ2015-69136-R) and DEC Generalitat de Catalunya (Grant 2014SGR827). We also thank MINECO for a Severo Ochoa Excellence Accreditation 2014–2018 (SEV-2013-0319).

Notes and references

† Not even traces of the cyclized product have been obtained with any of the catalysts tested in this work; addition of an external base was necessary to obtain **8**. To the best of our knowledge, this is the first time that **7a** has been isolated and characterized, including an X-ray structure (CCDC 1456999).‡

‡ See Electronic Supporting Information (ESI) for details.

§ See section 7 of the ESI for a proposed stereochemical model.

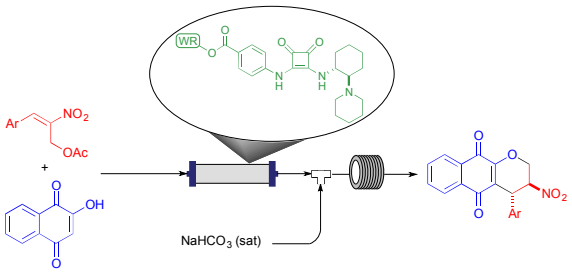
§§ This solution had to be diluted with respect to the batch conditions and a small portion of THF had to be added in order to fully solubilize the hydroxynaphthoquinone.

1. F. Darvas, V. Hessel and G. Dorman (Eds.), *Flow Chemistry, Volume 1 Fundamentals*, De Gruyter, Berlin, 2014.
2. (a) J. Izquierdo and M. A. Pericàs, *ACS Catalysis*, 2016, **6**, 348-356; (b) R. Porta, M. Benaglia and A. Puglisi, *Org. Process Res. Dev.*, 2016, **20**, 2-25; (c) I. Sagamanova, C. Rodríguez-Escrich, I. G. Molnár, S. Sayalero, R. Gilmour and M. A. Pericàs, *ACS Catalysis*, 2015, **5**, 6241-6248; (d) P. Kasaplar, E. Ozkal, C. Rodríguez-Escrich and M. A. Pericàs, *Green Chem.*, 2015, **17**, 3122-3129; (e) I. Atodiresei, C. Vila and M. Rueping, *ACS Catalysis*, 2015, **5**, 1972-1985; (f) R. Munirathinam, J. Huskens and W. Verboom, *Adv. Synth. Catal.*, 2015, **357**, 1093-1123; (g) C. Rodríguez-Escrich, *Chim. Oggi*, 2015, **33**, 12-15; (h) S. B. Ötvös, A. Szloszár, I. M. Mándity and F. Fülöp, *Adv. Synth. Catal.*, 2015, **357**, 3671-3680; (i) C. Rodríguez-Escrich and M. A. Pericàs, *Eur. J. Org. Chem.*, 2015, 1173-1188; (j) A. Puglisi, M. Benaglia and V. Chiroli, *Green Chem.*, 2013, **15**, 1790-1813; (k) T. Tsubogo, T. Ishiwata and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2013, **52**, 6590-6604; (l) G. Kardos and T. Soós, *Eur. J. Org. Chem.*, 2013, 4490-4494.
3. P. Kasaplar, P. Riente, C. Hartmann and M. A. Pericàs, *Adv. Synth. Catal.*, 2012, **354**, 2905-2910.
4. P. Kasaplar, C. Rodríguez-Escrich and M. A. Pericàs, *Org. Lett.*, 2013, **15**, 3498-3501.
5. (a) A. Bastero, D. Font and M. A. Pericàs, *J. Org. Chem.*, 2007, **72**, 2460-2468; (b) L. Osorio-Planes, C. Rodríguez-Escrich and M. A. Pericàs, *Chem. Eur. J.*, 2014, **20**, 2367-2372.
6. (a) D. K. Nair, R. F. S. Menna-Barreto, E. N. da Silva Júnior, S. M. Mobin and I. N. N. Namboothiri, *Chem. Commun.*, 2014, **50**, 6973-6976; (b) G. A. M. Jardim, T. T. Guimarães, M. C. F. R. Pinto, B. C. Cavalcanti, K. M. de Farias, C. Pessoa, C. C. Gatto, D. K. Nair, I. N. N. Namboothiri and E. N. da Silva Júnior, *MedChemComm*, 2015, **6**, 120-130.
7. (a) A. Fujiwara, T. Mori, A. Iida, S. Ueda, Y. Hano, T. Nomura, H. Tokuda and H. Nishino, *J. Nat. Prod.*, 1998, **61**, 629-632; (b) P. Krishnan and K. F. Bastow, *Biochem. Pharmacol.*, 2000, **60**, 1367-1379; (c) A. J. M. da Silva, C. D. Netto, W. Pacienza-Lima, E. C. Torres-Santos, B. Rossi-Bergmann, S. Maurel, A. Valentin and P. R. R. Costa, *J. Braz. Chem. Soc.*, 2009, **20**, 176-182; (d) R. L. Fabri, R. M. Grazul, L. O. de Carvalho, E. S. Coimbra, G. M. M. Cardoso, E. M. de Souza-Fagundes, A. D. da Silva and E. Scio, *An. Acad. Bras. Cienc.*, 2012, **84**, 1081-1090.
8. T. T. Guimarães, M. C. F. R. Pinto, J. S. Lanza, M. N. Melo, R. L. do Monte-Neto, I. M. M. de Melo, E. B. T. Diogo, V. F. Ferreira, C. A. Camara, W. O. Valenca, R. N. de Oliveira, F. Frezard and E. N. da Silva Júnior, *Eur. J. Med. Chem.*, 2013, **63**, 523-530.
9. M. A. Brimble, M. R. Nairn and H. Prabaharan, *Tetrahedron*, 2000, **56**, 1937-1992.

Graphical and Textual Abstract

A new, cost-effective polystyrene-supported squaramide organocatalyst mediates the completely diastereoselective and highly enantioselective formation of pyranonaphthoquinones in flow through a sequential two-step process involving a squaramide-catalyzed Michael reaction and an oxa-Michael cyclization.

ChemDraw file:



Tif file: