Organocatalytic Enantioselective Aminoalkylation of 5-Aminopyrazole derivatives with Cyclic Imines

Laura Carceller-Ferrer,[a] Aleix González del Campo,[a] Carlos Vila,[a] Gonzalo Blay,*[a] M. Carmen Muñoz[b] and José R. Pedro*[a]

Abstract: In this communication, an efficient asymmetric aminoalkylation of 5-aminopyrazole derivatives with cyclic benzoxathiazine 2,2-dioxides catalyzed by a quinine-derived squaramide in dichoromethane has been established. This is the first example of 5-aminopyrazole derivatives in asymmetric catalysis. A variety of chiral sulfamidates bearing an aminopyrazole moiety were obtained in good yields (up to 98%) and moderate to excellent enantioselectivities (up to 99%ee).

Introduction

Heterocycles are fundamental in chemistry and have received the attention of the synthetic community for many decades, because they exhibit a wide range of applications in pharmaceutical, medicinal and agrochemical chemistry as well as in material science. In this context, nitrogen heterocycles[1] are the most common and important class of heterocycles, present in uncountable biologically active compounds and are very important for drug design in pharmaceutical industry. For example, in the FDA data base, 60% of small-molecule drugs contain a nitrogen heterocycle.[2] In this regard, pyrazole derivatives represent one of the most important nitrogen heterocycles existing in blockbuster drugs, and consequently their derivatives have been studied extensively for the last decades.[3] For example, 5-aminopyrazoles have recently gained widespread attention and occupies a great position because of its biological and medicinal features as well as its synthetic versatility.[4] This kind of scaffold is present in several compounds with biological activities such as antifungal,[5] antibacterial[6] among others[7] (Figure 1A). The synthetic versatility of 5-aminopyrazoles is very remarkable, because of the presence of several nucleophilic positions, making them a synthetic challenge in order to obtain regioselectivity. The versatility of 5-aminopyrazoles has made them very interesting scaffolds for the synthetic community and medicinal chemistry, and several reports have been described showing their electrophilic functionalization.[4] Despite of this, to the best of our knowledge, the catalytic enantioselective functionalization of 5-aminopyrazoles is unknown. Therefore, as a part of our ongoing interest in organocatalytic enantioselective functionalization of nitrogen heterocycles,[8] we become interested in study the use of this kind of nitrogen heterocycles as nucleophiles in asymmetric catalysis. It is noteworthy that the development of such enantioselective functionalization of this pyrazole derivative could be interesting for pharmaceutical and medicinal chemistry.

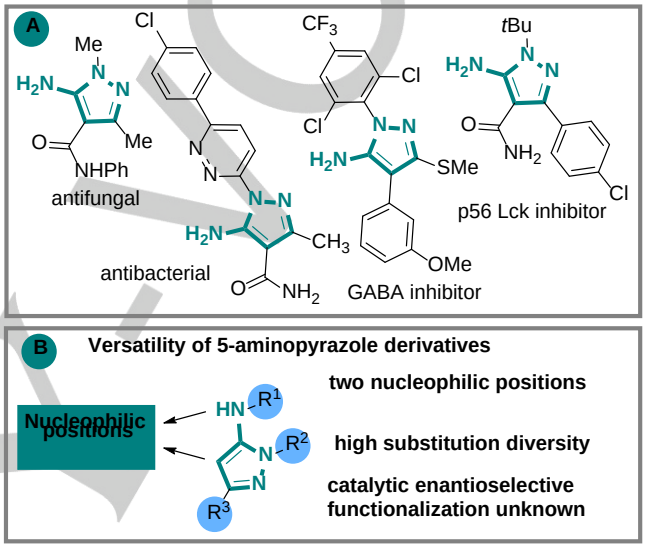


Figure 1. A) Some biologically active molecules containing 5-aminopyrazole moiety. B) Versatility of 5-aminopyrazole derivatives.

Herein, we report the organocatalytic enantioselective aminoalkylation of 1-substituted-1*H*-pyrazol-5-amines using benzoxathiazine 2,2-dioxides as electrophiles. Recently, this class of cyclic imines have attracted attention in asymmetric catalysis,[9,10] because these compounds have been proved to be powerful building blocks for the synthesis of chiral benzosulfamidate heterocycles. In this context, several sulfamidates have shown important biological activities[11] and several examples of enantioselective reactions have been described using these cyclic imines as electrophiles.

Results and Discussion

We chose the aminoalkylation reaction between benzoxathiazine 2,2-dioxides (**1a**) and 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**2**) for the optimization studies in the presence of cinchona alkaloid-derived squaramide organocatalysts (Table 1).[12,13] When the quinine-derived squaramide **A** was used as a catalyst we observed a promising enantioselectivity (49% ee, entry 1). When **B**, the quinine-derived squaramide bearing a benzyl group, was used product **3aa** was obtained with an improvement on the enantiomeric excess to 62% (entry 2). However, when the quinine-derived squaramide **C** or **D** were used, we observed a decrease on the enantiomeric excess of pyrazole derivative **3aa**

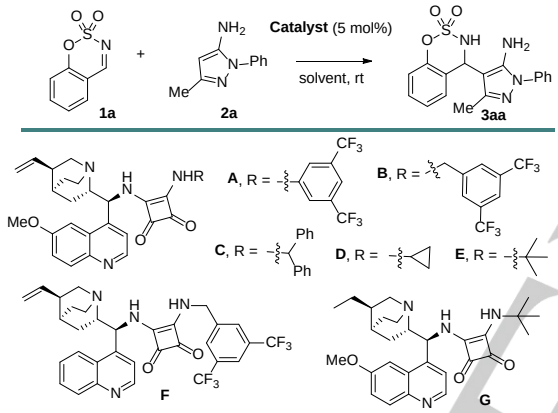
[a] L. Carceller-Ferrer, A. González del Campo, Dr. C. Vila, Prof. Dr. G. Blay, Prof. Dr. J. R. Pedro
Departament de Química Orgànica, Facultat de Química, Universitat de València, Dr. Moliner 50, 46100 Burjassot, València (Spain)
E-mail: gonzalo.blay@uv.es; jose.r.pedro@uv.es

[b] Prof. Dr. M. C. Muñoz
Departament de Física Aplicada, Universitat Politècnica de València, Camino de Vera s/n, 46022 València (Spain)

Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

(40% ee and 45% ee, entry 3 and 4). Squaramide **E**, with a *tert*-butyl group, yield a slightly increase on the enantioselectivity of the reaction (entry 5), obtaining the corresponding chiral sulfamidate with 83% yield and 65% ee. Cinchonidine-derived squaramide **F**, afford the product **3aa** with good yield but lower enantioselectivity. Lastly, when catalyst **G**, the dihydroquinine-derived squaramide, was used we observed also lower enantiomeric excess for the chiral product **3aa** (48% ee, entry 6). Therefore, we chose catalyst **E** to continue the optimization process of the reaction conditions, including solvents or temperatures. Different solvents were then tested (Table 1, entries 8-13), however we could not improve the results obtained when CH_2Cl_2 was used as a solvent (entry 5). Finally, different temperatures were tested. By lowering the reaction temperature to 4 °C (entry 14), the enantioselectivity of the reaction decreased to 51% ee with a moderate yield (56%). While increasing the temperature of the reaction to 30 °C, also decreased the enantiomeric excess of **3aa**.

Table 1. Optimization of the reaction conditions.

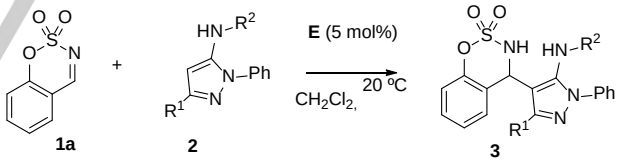


Entry[a]	Catalyst	Solvent	t (h)	Yield (%)[b]	ee (%) [c]
1	**A** (5 mol %)	CH_2Cl_2	5	86	49
2	**B** (5 mol %)	CH_2Cl_2	12	95	62
3	**C** (5 mol %)	CH_2Cl_2	24	70	40
4	**D** (5 mol %)	CH_2Cl_2	5	95	45
5	**E** (5 mol %)	CH_2Cl_2	12	83	65
6	**F** (5 mol %)	CH_2Cl_2	24	80	46
7	**G** (5 mol %)	CH_2Cl_2	24	88	48
8	**E** (5 mol %)	DCE	5	96	57
9	**E** (5 mol %)	$CHCl_3$	5	96	50
10	**E** (5 mol %)	toluene	5	83	20
11	**E** (5 mol %)	Et_2O	5	73	10
12	**E** (5 mol %)	EtOAc	5	73	33
13	**E** (5 mol %)	CCl_4	4	76	10
14[d]	**E** (5 mol %)	CH_2Cl_2	24	56	51
15[e]	**E** (5 mol %)	CH_2Cl_2	2	99	56

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol) and catalyst (5 mol%) in 1 mL of solvent at 20 °C. [b] Isolated yield after column chromatography. [c] Determined by HPLC using chiral stationary phase. [d] The reaction was performed at 4 °C. [e] The reaction was performed at 30 °C. DCE= $ClCH_2CH_2Cl$.

At this point of the optimization, we evaluate the substitution pattern of the 5-aminopyrazole **2** to study the effect of the groups on the reactivity and enantioselectivity of the reaction (Table 2). We observed that when we use the 5-aminopyrazole **2b**, bearing a phenyl group at 3 position, we observed a decreased in the reactivity (93% yield, after 6 days) and a reduction in the enantioselectivity (27% ee). At this point we decide to study the effect of the substitution of the amine in the aminoalkylation reaction. *N*-benzyl-3-methyl-1-phenyl-1*H*-pyrazol-5-amine **2c**, gave the chiral sulfamidate **3ac** with excellent yield (97%) but lower enantioselectivity (59% ee). In contrast, 3-methyl-*N*,1-diphenyl-1*H*-pyrazol-5-amine **2d** bearing a phenyl protecting group at the nitrogen of the amine, gave better enantiomeric excess (83% ee), and good yield (83%) but with 6 days of reaction time. Finally, when *N*,1,3-triphenyl-1*H*-pyrazol-5-amine **2e** the corresponding product was obtained with very low yield (16%), after 10 days, and low enantioselectivity (32% ee). Therefore, we decide to continue the optimization process using 5-amino-pyrazole derivative **2d**, that gave the best results in terms of yield and enantioselectivity. We decide to increase the catalyst loading to 10 mol% (entry 6), but unfortunately lower enantiomeric excess for product **3ad** was observed.

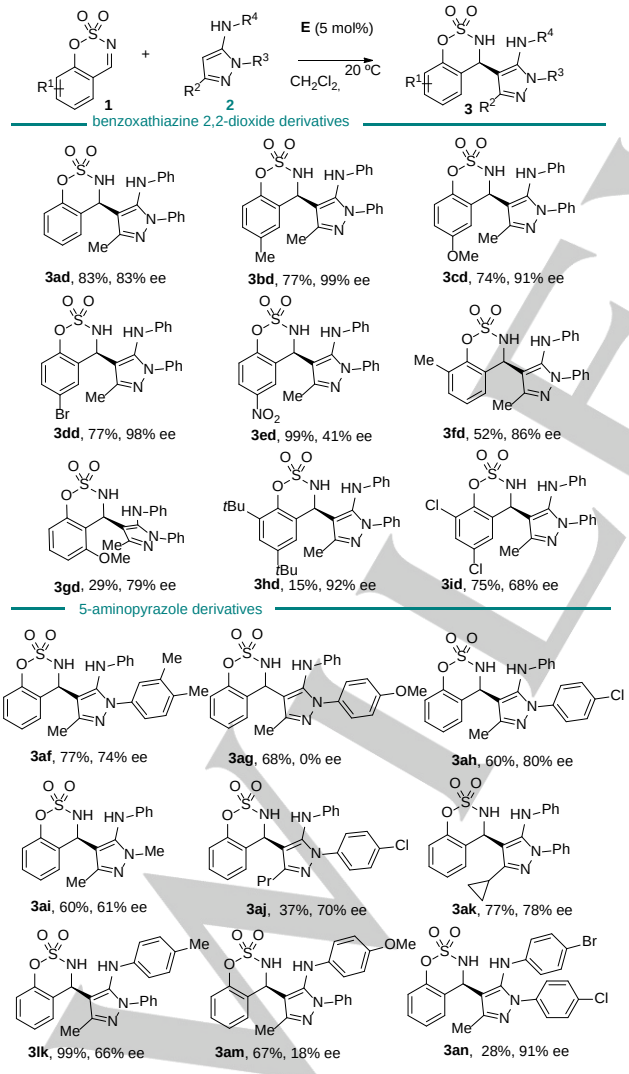
Table 2. Optimization of the reaction conditions.



Entry[a]	R^1	R^2	**2**	t (d)	**3**	Yield (%)[b]	Ee (%) [d]
1	Me	H	**2a**	0.5	**3aa**	83	65
2	Ph	H	**2b**	6	**3ab**	93	27
3	Me	CH_2Ph	**2c**	4	**3ac**	97	59
4	Me	Ph	**2d**	6	**3ad**	83	83
5	Ph	Ph	**2e**	10	**3ae**	16	32
6	Me	Ph	**2d**	6	**3ad**	84	76

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol) and catalyst (5 mol%) in 1 mL of CH_2Cl_2 at 20 °C. [b] Isolated yield after column chromatography. [c] Determined by HPLC using chiral stationary phase. [d] The reaction was performed with 10 mol% of E.

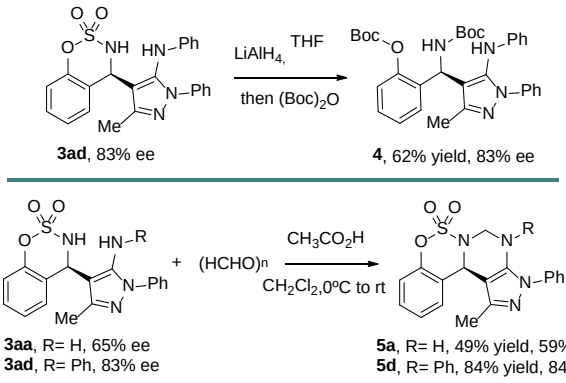
With the optimized reaction conditions in hand, the scope of the aminoalkylation reaction was studied (Scheme 1). First, we evaluate the versatility of the benzoxathiazine 2,2-dioxides with 5-amino-pyrazole **2d**. Various substituents in the 6-position in the phenyl ring of the cyclic imines **1**, such as Me, MeO, Br or NO_2, were well tolerated under the reaction conditions, and the corresponding chiral sulfamidates **3** were obtained with good yields (74–99 %) and in general high enantioselectivities (83–99 %), although the presence of a NO_2 group decreases the enantiomeric excess to 41% ee. A cyclic imine bearing a substituent in the 8 position gave product **3fd** in 52% yield and 86% ee. However, the presence of a methoxy group in the 5 position led to a high decrease in the reactivity (29% yield), but with good enantioselectivity (79% ee). Furthermore, cyclic imines (**1h-1i**) with two substituents that provide steric hindrance, were tested in the amino alkylation reaction. The presence of highly steric groups such as *t*Bu group reduces the reactivity (15% yield) maintaining the enantioselectivity, however if the groups are chlorine atoms the product **3id** is obtained with good yield (75%) but lower enantiomeric excess (68 % *ee*).



Scheme 1. Scope of the aminoalkylation of 5-aminopyrazoles **2** with cyclic imines **1**. Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol) and **E** (5 mol%) in 1 mL of CH_2Cl_2 at 20 °C for 6 days. Isolated yield after column chromatography. Enantiomeric excess determined by HPLC using chiral stationary phase.

We next turned our attention to further investigate the substrate scope with respect to the 5-aminopyrazoles **2**. First we evaluate the effect of the substituents at the aromatic ring *N*-1 of the 5-aminopyrazoles (**3af**-**3ah**). The reaction proceeded with good yields and good enantioselectivities when the substituents at the aromatic ring of *N*-1 are Me or Cl. However, the presence of a MeO group at the aromatic ring of *N*-1 had a strong influence obtaining the product as a racemic mixture. 1,3-dimethyl-*N*-phenyl-1*H*-pyrazol-5-amine could be used as nucleophile, although with moderate levels of enantioselectivity. Other alkyl groups than Me are tolerated at the 3 position of the 5-aminopyrazoles (**3aj**-**3ak**). Finally, we evaluate the effect of the substituents at the exocyclic nitrogen. The presence of electron-donating groups Me or MeO) decreases the enantioselectivity maintaining good yields, while electron-withdrawing groups (Cl) increases the enantiomeric excess (91% ee) although the conversion is low.

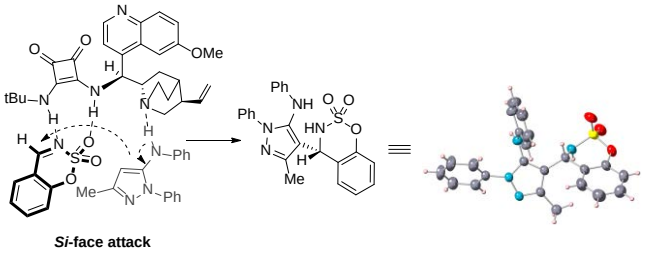
Furthermore, we performed several synthetic transformations with the chiral aminopyrazoles **3** (Scheme 4). We carried out the reduction of the sulfamidate moiety[11p] of compound **3ad** using $LiAlH_4$ obtaining the corresponding chiral amine bearing a phenol and aminopyrazole moieties, which was protected *in situ* as its Boc derivative **4**, with good yield (62%) and preserving the enantiomeric excess of compound **3ad** (83% ee). Finally, treatment of compounds **3aa** and **3ad** with paraformaldehyde under acidic conditions led the formation of aminopyrazole-sulfamidate fused tetracycle compounds **5a** and **5d** with good yields and maintaining the enantiomeric excess (Scheme 2).



Scheme 2. Synthetic transformations of chiral 5-aminopyrazoles.

The absolute configuration of the stereogenic centre in compound **3ad** was determined to be (*S*) on the basis of X-ray crystallographic analysis (Scheme 3); the configurations of the rest of the products **3** were assigned on the assumption of a uniform mechanistic pathway.[14] A plausible transition-state model is depicted in Scheme 5. The chiral squaramide acts as

bifunctional organocatalyst responsible for the preorientation and the activation of the substrates. While the benzoxathiazine is activated upon formation of hydrogen bonds between the nitrogen and one oxygen of the cyclic imine and the squaramide,[15] the 5-aminopyrazole undergoes nucleophilic activation by hydrogen bonding with the quinuclidine moiety of the catalyst. The nucleophilic attack of the 5-aminopyrazole will be directed to the *Si*-face of the cyclic imine, thus accounting for the observed enantioselectivity. The low conformational mobility and the impossibility of *E*/*Z* isomerization of the double bond of the imine **1** is very important for the enantioselectivity of the reaction. When the reaction was performed with *N*-tosylimine prepared from benzaldehyde the reaction took place with good yield (72%) but as a racemic mixture after 2 days of reaction.



Scheme 3. X-ray structure of **3ad** and plausible transition-state model.

Conclusions

In conclusion, we have successfully developed an organocatalytic enantioselective aminoalkylation of 5-aminopyrazole derivatives with cyclic imines using a quinine-derived squaramide organocatalyst, obtaining the corresponding chiral sulfamidates bearing a 5-aminopyrazole moiety with good yields (up to 97%) and moderate to excellent enantioselectivities (up to 99% ee) under mild reaction conditions. Studies to further extend the scope of this reaction are currently underway in our laboratory.

Acknowledgements

Financial support from the Agencia Estatal de Investigación (AEI, Spanish Government) and Fondo Europeo de Desarrollo Regional (FEDER, European Union) (CTQ2017-84900-P) is acknowledged. L. C. thanks the Universitat de València for a predoctoral grant. C.V. thanks the Spanish Government for RyC contract (RYC-2016-20187). Access to NMR, MS and X-ray facilities from the Servei Central de Suport a la Investigació Experimental (SCSIE)-UV is also acknowledged.

Keywords: asymmetric catalysis • nitrogen heterocycles • pyrazoles • organocatalysis • cyclic imines

[1] a) *Advances in Nitrogen Heterocycles*, C. J. Moody, Ed. AI Press LTD., London, **1999**; b) *Asymmetric Synthesis of Nitrogen Heterocycles*, J. Royer, Ed. Wiley-VCH, Weinheim, **2009**.

[2] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem*. **2014**, *57*, 10257-10274.

[3] a) A. Schmidt, A. Dreger, *Curr. Org. Chem*. **2011**, *15*, 1423-1463; b) S. Fustero, M. Sánchez-Roselló, P. Barrio, A. Simón-Fuentes, *Chem. Rev*. **2011**, *111*, 6984-7034; c) V. Kumar, K. Kaur, G. K. Gupta, A. K. Sharma, *Eur. J. Med. Chem*. **2013**, *69*, 735-753.

[4] a) H. F. Anwar, M. H. Elnagdi, *ARKIVOC* **2009**, 198-250; b) R. Aggarwal, V. Kumar, R. Kumar, S. P. Singh, *Beilstein J. Org. Chem*. **2011**, *7*, 179-197; c) R. Aggarwal, S. Kumar, *Beilstein J. Org. Chem*. **2018**, *14*, 203-242; d) A. Shaabani, M. T. Nazeri, R. Afshari, *Molecular Diversity*, **2019**, *23*, 751-807.

[5] a) J. L. Huppatz, *Aust. J. Chem.* **1985**, *38,* 221-230; b) P. Giori, M. Guarneri, D. Mazzota, G. Vertuani, C. Branca, *Farmaco Sci*. **1979**, *34*, 277-283; c) C. B. Vicentini, T. Poli, M. Manfrini, M. Guarneri, P. Giori, V. Brandolini, *Farmaco Sci*, **1987**, *42*, 133-143.

[6] a) S. T. Moe, A. B. Thompson, G. M. Smith, R. A. Fredenburg, R. L. Stein, A. R. Jacobson, *Bioorgan. Med. Chem*. **2009**, *17*, 3072-3079; b) K. S. Gudmundsson, B. A. Johns, J. Weatherhead, *Bioorgan. Med. Chem. Lett*. **2009**, *19*, 5689-5692; c) A. H. Shamroukh, A. E. Rashad and H. H. Sayed, *Phosphorus, Sulfur Silicon Relat. Elem.* **2005,** *180,* 2347-2360; d) M. H. Helal, M. A. Salem, H. Aly, *J. Heterocyclic Chem*. **2017**, *54*, 2614-2626.

[7] a) J. E. Ancel, L. El Kam, A. Gadras, L. Grimaud, N. K. Jana, *Tetrahedron Lett*. **2002**, *43*, 8319-8321; b) J. Tang, L. M. Shewchuk, H. Sato, M. Hasegawa, Y. Washio, N. Nishigaki, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 2985-2988; c) J. Das, R. V. Moquin, A. J. Dyckman, T. Li, S. Pitt, R. Zhang, D. R. Shen, K. W. McIntyre, K. Gillooly, A. M. Doweyko, J. A. Newitt, J. S. Sack, H. Zhang, S. E. Kiefer, K. Kish, M. McKinnon, J. C. Barrish, J. H. Dodd, G. L. Schieven, K. Leftheris, *Bioorg. Med. Chem. Lett*. **2010**, *20*, 6886-6889; d) C. W. Lindsley, D. D. Wisnoski, W. H. Leister, J. A. O'Brien, W. Lemaire, D. L. Williams, M. Burno, C. Sur, G. G. Kinney, D. J. Pettibone, *J. Med. Chem*., **2004**, *47*, 5825-5828; e) T. A. Carter, L. M. Wodicka, N. P. Shah, A. M. Velasco, M. A. Fabian, D. K. Treiber, Z. V. Milanov, C. E. Atteridge, W. H. Biggs, P. T. Edeen, M. Floyd, J. M. Ford, R. M. Grotzfeld, S. Herrgard, D. E. Insko, S. A. Mehta, H. K. Patel, W. Pao, C. L. Sawyers, H. Varmus, P. P. Zarrinkar, D. Lockhart, *Proc. Natl. Acad. Sci. U. S. A.* **2005**, *102,* 11011-11016.

[8] a) L. Carceller-Ferrer, C. Vila, G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro, *Org. Biomol. Chem*., **2019**, *17*, 9859-9863; b) F. I. Amr, C. Vila, G. Blay, M. C. Muñoz, J. R. Pedro, *Adv. Synth. Catal*. **2016**, *358*, 1583-1588; c) C. Vila, F. I. Amr, G. Blay, M. C. Muñoz, J. R. Pedro, *Chem.–Asian J.* **2016**, *11*, 1532-1536; d) C. Vila, S. Slack, G. Blay, M. C. Muñoz, J. R. Pedro, *Adv. Synth. Catal.* **2019**, *361*, 1902-1907; e) C. Vila, N. Raj Dharmaraj, A. Faubel, G. Blay, M. L. Cardona, M. C. Muñoz, J. R. Pedro, *Eur. J. Org. Chem.* **2019**, 3040-3044.

[9] L. De Munck, C. Vila, J. R. Pedro, in *Targets in Heterocyclic Chemistry*, Ed. O. A. Attanasi, P. Merino and D. Spinelli, Società Chimica Italiana, **2017**, p. 137.

[10] a) J.-Y. Winum, A. Scozzafava, J.-L. Montero, C. T. Supuran, *Med. Res. Rev.*, **2005**, *25*, 186-228; b) S. R. Hanson, L. J. Whalen, C.-H. Wong, *Bioorg. Med. Chem*., **2006**, 8386-8395; c) S. J. Kim, H. B. Park, J. S. Lee, N. H. Jo, K. H. Yoo, D. Baek, B.-W. Kang, J.-H. Cho, C.-H. Oh, *Eur. J. Med. Chem*., **2007**, 1176-1183; d) S. J. Kim, M.-H. Jung, K. H. Yoo, J.-H. Cho, C.-H. Oh, *Bioorg. Med. Chem. Lett*., **2008**, 5815-5818; e) B. Wei, J. Zhou, J.-J. Xu, J. Cui, F.-F. Ping, J.-J. Ling, Y.-J. Chen, *Eur. J. Med. Chem*., **2019**, *184*, 111779.

[11] Selected examples: a) H. Wang, T. Jiang, M.-H. Xu, *J. Am. Chem. Soc*. **2013**, *135*, 971-974; b) C. Jiang, Y. Lu, T. Hayashi, *Angew. Chem. Int. Ed*. **2014**, *53*, 9936-9939; c) H. B. Hepburn, H. W. Lam, *Angew. Chem. Int. Ed*. **2014**, *53*, 11605-11610; d) Y. Luo, H. B. Hepburn, N. Chotsaeng, H. W. Lam, *Angew. Chem. Int. Ed*. **2012**, *51*, 8309-8313; e) J. I. Martínez, J. J. Smith, H. B. Hepburn, H. W. Lam, *Angew. Chem. Int. Ed*. **2016**, *55*, 1108-1112; f) Y.-Q. Wang, X.-Y. Cui, Y.-Y. Ren, Y. Zhang, *Org. Biomol. Chem*. **2014**, *12*, 9101-9104; g) H.-X. Zhang, J. Nie, H. Cai, J.-A. Ma, *Org. Lett*. **2014**, *16*, 2542-2545; h) C.-M. Jia, H.-X. Zhang, J. Nie, J.-A. Ma, *J. Org. Chem*. **2016**, *81*, 8561-8569; i) Y. Liu, T.-R. Kang, Q.-Z. Liu, L.-M. Chen, Y.-C. Wang, J. Liu, Y.-M. Xie, J.-L. Yang, L. He, *Org. Lett.*

2013, *15*, 6090-6093; j) L. Zhang, H. Yu, Z. Yang, H. Liu, Z. Li, J. Guo, Y. Xiao, H. Guo, *Org. Biomol. Chem*. **2013**, *11*, 8235-8240; k) S. G. Lee, S.-G. Kim, *RSC Adv*., **2017**, *7*, 34283-34286; l) J. Kim, M. Shin, S. H. Cho, *ACS Catal*. **2019**, *9*, 8503-8508. Examples from our group: m) L. De Munck, A. Monleón, C. Vila, M. C. Muñoz, J. R. Pedro, *Org. Biomol. Chem.*, **2015**, *13*, 7393-7396; n) M. Montesinos-Magraner, R. Cantón, C. Vila, G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro, *RSC Adv*., **2015**, *75*, 60101-60105; o) L. De Munck, C. Vila, M. C. Muñoz, J. R. Pedro, *Chem. Eur. J.* **2016**, *22*, 17590-17594; p) L. De Munck, A. Monleón, C. Vila, J. R. Pedro, *Adv. Synth. Catal*., **2017**, *359,* 1582-1587; q) C. Vila, A. Tortosa, G. Blay, M. C. Muñoz, J. R. Pedro, *New J. Chem*., **2019**, *43*, 130-134.

[12] For further optimization of organocatalyst see the supporting information.

[13] a) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890-6899; b) B.-L. Zhao, J.-H. Li, D.-M. Du, *Chem. Rec.* **2017**, *17*, 994-1018. For reports using quinine-derived squaramides with a *t*ert-butyl unit, please see: c) F. Manoni, S. J. Connon, *Angew. Chem. Int. Ed*. **2014**, *126*, 2666-2670; d) E. Kanberoğlu, C. Tanyeli, *Asian J. Org. Chem.*, **2016**, *5*, 114-119; e) D. Susam, C. Tanyeli, *New J. Chem.* **2017**, *41*, 3555-3561.

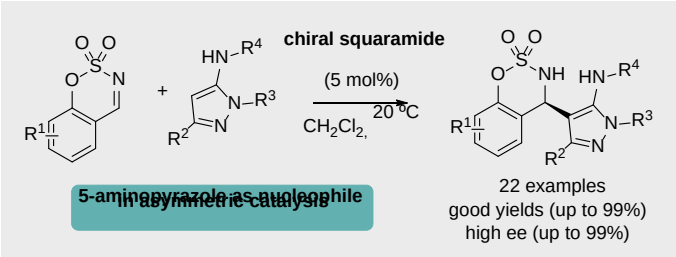
[14] CCDC 2024661 (**3ad**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[15] Benzoxathiazine can also make different hydrogen bonds with the chiral bifunctional organocatalyst, however we have hypothesized the cyclic transition state-model that have been previously described in the literature, see references: 11k, 11n and 11q.

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION



Organocatalytic Enantioselective Aminoalkylation of 5-Aminopyrazole derivatives with Cyclic Imines

Laura Carceller-Ferrer,[a] Aleix González del Campo,[a] Carlos Vila,[a] Gonzalo Blay,[a] M. Carmen Muñoz[b] and José R. Pedro*[a]*

Page No. – Page No.

The first enantioselective alkylation of 5-aminopyrazoles is described with good results. The organocatalytic alkylation of 5-aminopyrazoles have been acomplished using benzoxathiazine 2,2-dioxides as electrophiles and a bifunctional squaramide organocatalyst.

*one or two words that highlight the emphasis of the paper or the field of the study: **Organocatalysis**