

Organocatalytic Enantioselective Aminoalkylation of Pyrazol-3-ones with Aldimines Generated *in Situ* from α -Amido Sulfones

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Herein, an efficient asymmetric aminoalkylation of pyrazolones with α -amido sulfones catalyzed by a quinine-derived squaramide in dichloromethane/aqueous media has been established. A variety of chiral amines were obtained in high yields (up to 98%) and excellent enantioselectivities (up to 99%ee). The corresponding products are transformed in optically active acetylated pyrazoles after treatment with $\text{Ac}_2\text{O}/\text{Et}_3\text{N}$, because of the instability of some adducts. The reaction tolerates a wide range of α -amido sulfones as well as different pyrazolones.

Introduction

Nitrogen heterocycles are extremely important in chemistry, because an enormous number of aza-heterocycles exhibit a variety of applications in pharmaceutical, medicinal and agrochemical chemistry as well as in material science.¹ In this context, pyrazolone derivatives,² containing two contiguous nitrogen atoms, are a privileged class of nitrogen heterocycles, and several pharmaceutical and agrochemical compounds have this scaffold in their structure (Figure 1). For example, the pyrazolone scaffold is present in analgesics such as phenazone,³ neuroprotective agents such as edavorone,⁴ or other biological active compounds such as remogliflozin etabonate⁵ or dihydropyrano[2,3-*c*]pyrazole derivative **Pyr-4**, which is a human Chk1 kinase inhibitor.⁶ Owing to the broad biological activities of pyrazolones, these compounds have been used in asymmetric catalysis as nucleophiles for the synthesis of new potentially bioactive enantiopure pyrazolone and pyrazole derivatives.⁷

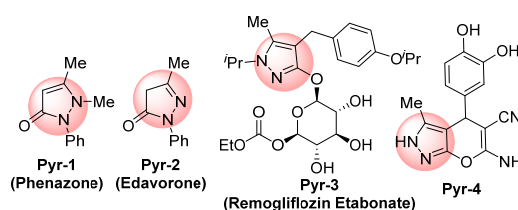


Figure 1 Some biologically active molecules containing pyrazolone/pyrazole moieties.

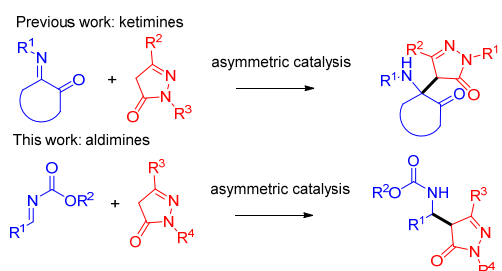
On the other hand, chiral amines are particularly important building blocks for asymmetric synthesis of natural products, fine chemicals and pharmaceutical compounds.⁸ Consequently, the development of efficient methodologies for the enantioselective synthesis of chiral amines represents a central topic in organic synthesis.⁹ Given the relevance of pyrazolone moiety and amine groups, it was anticipated that the incorporation of both structural motifs into one molecule could result in novel chiral amines bearing a pyrazolone moiety with potentially biological activities.¹⁰ To date several enantioselective additions of pyrazol-3-ones to isatin derived ketimines¹¹ and pyrazolone-derived ketimines¹² have been described in the literature (Scheme 1). However, the corresponding asymmetric addition of pyrazolones to aldimines have not been reported, to the best of our knowledge. This fact could be attributed to the lack of stability of the corresponding imines or the final chiral products. A possible solution to this problem could be the generation *in situ* of the imine using of α -amido sulfones.¹³ α -Amido sulfones are suitable precursors of imines because they react with basic reagents by deprotonation of the carbamate and elimination of the sulfinate group to give *N*-carbamoyl imines. Advantageously, α -amido sulfones are stable solids that can be readily obtained in one-step reaction by condensation of carbamates and sodium aryl sulfonates with aldehydes. In fact, several enantioselective methodologies have been described for the synthesis of chiral amines using α -amido sulfones as electrophiles.¹⁴ Thus, we envisioned that this kind of precursors could be used on the asymmetric aminoalkylation of pyrazol-3-ones.

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As a part of our ongoing interest in the stereoselective synthesis of pyrazolones,^{11b-c,15} herein we described the enantioselective addition of pyrazol-3-ones to aldimines, generated *in situ* from α -amido sulfones, providing a novel chiral pyrazole adducts after acetylation of the pyrazolone moiety.



Scheme 1 Asymmetric aminoalkylation of pyrazolones with imines.

Results and discussion

Our initial studies were focused on the enantioselective aminoalkylation of 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**2a**) with benzyl (phenyl(phenylsulfonyl)methyl)carbamate (**1a**) in the presence of bifunctional organocatalysts.^[16] We chose cinchona alkaloid-derived catalysts, in which the tertiary amine should promote both the imine formation by sulfonic acid elimination and the nucleophile (pyrazol-3-one) activation. Besides the hydrogen bonding donor moiety (thiourea or squaramide groups respectively) should produce the activation of the *in situ* generated electrophile (the *N*-carbamoyl imine). The reactions were carried out in a biphasic system with dichloromethane as a solvent and potassium carbonate aqueous solution as an additional base.¹³ The results are shown in Table 1 (entries 1-5), which indicated the possibility of developing an enantioselective aminoalkylation of pyrazol-3-ones with all the evaluated catalysts. When the quinine thiourea derivative **A** was used as a catalyst we observed a promising enantioselectivity (76% ee, entry 1). When **B**, the quinine squaramide derivative, was used product **3a** was obtained with an enhancement on the enantiomeric excess to 85% (entry 2). However, when the quinidine squaramide derivative **C** was used, we observed a decrease on the enantiomeric excess of the opposite enantiomer of pyrazolone **3a** (70% ee, entry 3). Another quinine squaramide derivative catalyst **D**, also produce a decrease on the reactivity and enantioselectivity of the reaction (entry 4). Finally, when catalyst **E**, the dihydroquinine squaramide derivative, was used we observed the best enantiomeric excess for the chiral product **3a** (90% ee, entry 5). 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 5-9), obtaining the best results when the reaction was carried out in CH₂Cl₂/H₂O (2:1) (entry 5). Moreover, we tested the reaction with other inorganic bases obtaining better enantiomeric excess for compound **3a** (92% ee, entry 10) when Na₂CO₃ was used as a base although the yield was inferior. By

lowering the reaction temperature to 4 °C (entry 13), the enantioselectivity of the reaction increased to an excellent 98% ee and good yield (81%). Finally, we evaluate the influence of the sulfone leaving group (*p*ClC₆H₄SO₂- or Ts-, entries 14 and 15 respectively) obtaining similar yield (82% and 73%) and enantioselectivity (94% ee in both cases).

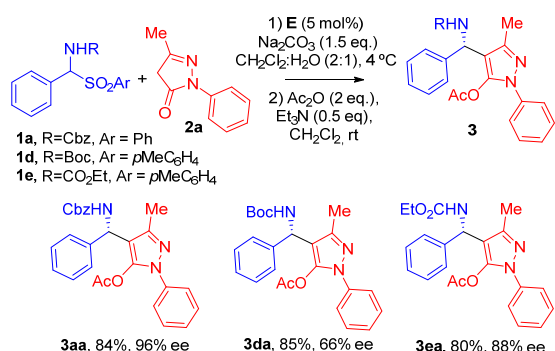
Table 1 Optimization of the reaction conditions.^a

Entry	Cat. (x mol%)	Solvent	t (h)	Yield (%) ^b	Ee (%) ^c
1	A (5 mol%)	CH ₂ Cl ₂	1	79	76
2	B (5 mol%)	CH ₂ Cl ₂	1	99	85
3	C (5 mol%)	CH ₂ Cl ₂	1	72	70 ^d
4	D (5 mol%)	CH ₂ Cl ₂	1	64	81
5	E (5 mol%)	CH ₂ Cl ₂	1	97	90
6	E (5 mol%)	ClCH ₂ CH ₂ Cl	1	55	83
7	E (5 mol%)	CHCl ₃	1	79	90
8	E (5 mol%)	toluene	1	63	89
9	E (5 mol%)	Et ₂ O	1	77	82
10 ^e	E (5 mol%)	CH ₂ Cl ₂	1	65	92
11 ^f	E (5 mol%)	CH ₂ Cl ₂	1	96	70
12 ^g	E (5 mol%)	CH ₂ Cl ₂	1	70	90
13 ^{e,g}	E (5 mol%)	CH ₂ Cl ₂	2	91	98
14 ^{e,g,h}	E (5 mol%)	CH ₂ Cl ₂	2	82	94
15 ^{e,g,i}	E (5 mol%)	CH ₂ Cl ₂	2	73	94

^a Reaction conditions: **1a** (0.15 mmol), **2a** (0.1 mmol), K₂CO₃ (1.5 eq.) and catalyst (5 mol%) in 1 mL of solvent and 0.5 mL of H₂O at rt. ^b Isolated yield after column chromatography. ^c Determined by HPLC using chiral stationary phase. ^d Opposite enantiomer was obtained. ^e The reaction was performed using Na₂CO₃ as a base. ^f The reaction was performed with **1b** (0.15 mmol). ^g The reaction was performed at 4 °C. ^h The reaction was performed with **1b** (0.15 mmol). ⁱ The reaction was performed with **1c** (0.15 mmol).

At this point of the optimization, we evaluate other α -amido sulfones bearing different *N*-protecting groups (Boc, COEt) (Scheme 2) to study the effect of the protecting group of the α -amido sulfone. We observed that the corresponding alkylated pyrazol-3-ones were not stable, and the analysis by NMR spectroscopy indicated that the addition product was a mixture of tautomers and diastereomers, that was difficult to analyse and describe. Fortunately, the corresponding chiral aminoalkylated pyrazol-3-one **3a** could be acetylated with Et₃N/Ac₂O, affording the corresponding pyrazole adduct **3aa** in 84 % yield and maintaining the enantiomeric excess (96% ee). In similar way, the α -amido sulfone **1d** bearing a Boc protecting group, gave the acetylated pyrazole **3da** with good yield (85% ee) but lower enantioselectivity (66% ee) than the Cbz protecting group. In contrast, the α -amido sulfone **1e** bearing a CO₂Et

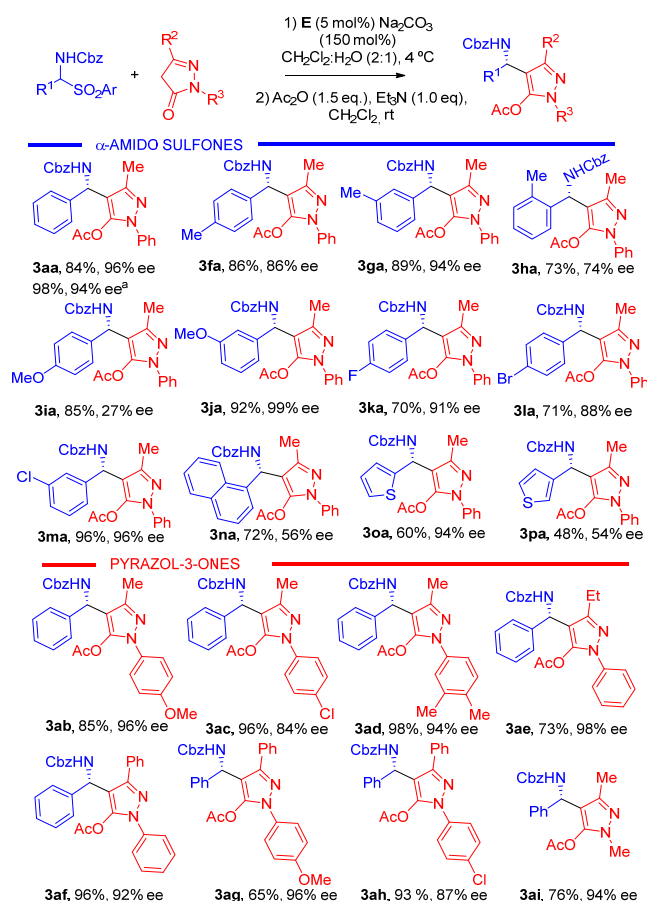
protecting group, gave better enantiomeric excess (88% ee), but still lower than the CO₂Bn protecting group.



Scheme 2. Evaluation of the protecting group of the α -amido sulfones **1**. Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), Na₂CO₃ (1.5 eq.) and **E** (5 mol%) in 1 mL of CH₂Cl₂ and 0.5 mL of H₂O at 4 °C. Isolated yield after column chromatography. Determined by HPLC using chiral stationary phase.

With the optimal conditions identified, the scope of the reaction was studied (Scheme 3). First, the versatility of the α -amido sulfones **1** was evaluated by using a series of *N*-benzyloxycarbonylsulfones derived from substituted benzaldehydes. The presence of a strong electron-donating group (MeO) at *para* position of the aromatic ring decreased the observed enantioselectivity (27% ee), while if the methoxy group is at *meta* position the corresponding chiral amine **3ja** is obtained with excellent yield (92%) and enantioselectivity (99% ee). Moreover, the reaction tolerates the presence of groups such Me, F, Cl or Br at *para* or *meta* position, obtaining the corresponding chiral acetylated pyrazoles **3** with good yields and high enantioselectivities (86–96% ee). However, when the methyl group is situated in the *ortho* position of the aromatic ring, the corresponding chiral amine **3ha** is obtained with good yield (73%) but an enantiomeric excess slightly lower (74% ee). The presence of a naphthyl substituent decrease the enantiomeric excess (56% ee). We also tested heteroaromatic α -amido sulfones that afforded the corresponding chiral amines with different levels of enantioselectivity depending on the position of the heteroatom. The α -amido sulfone prepared from thiophene-2-carbaldehyde afforded the product **3oa** with excellent enantioselectivity (94% ee), whereas when was used the α -amido sulfone prepared from thiophene-3-carbaldehyde the corresponding product **3pa** was obtained with moderate enantiomeric excess (54%). Different α -amido sulfones prepared from aliphatic aldehydes (3-phenylpropanal, cyclohexancarbaldehyde and 3,3-dimethylbutanal) were tested under the optimized reactions conditions, however we could not isolate the corresponding aminoalkylated pyrazolones **3**. We observed in the crude reaction mixture the presence of aldehydes, aldimines and some products derived from aldol reactions. We next turned our attention to further investigating the substrate scope with respect to the pyrazolones **2**. The reaction proceeded efficiently with pyrazolones with diverse substituents (MeO, Me or Cl) in the *N*-aryl group (**3ab–3ac**). 5-ethyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3ae**), could also be used obtaining the corresponding chiral amine with 73% yield and 98% ee. Moreover, when 2,5-diaryl-pyrazol-3-ones were tested the corresponding product **3af**, **3ag** and **3ah** were afforded with good yields (65–96%) and high enantioselectivities (87–96% ee). Finally,

2,5-dimethyl-pyrazolone **2i** was tested with α -amido sulfone **1a** leading to the corresponding products **3ai** with excellent results, both in yield (76%) and enantioselectivity (94% ee). Moreover, the reaction can be scale up to 1 mmol, obtaining product **3aa** in 98% yield and 94% ee.



Scheme 3. Scope of the Enantioselective alkylation of pyrazol-3-ones **2** with α -amido sulfones **1**. Reaction conditions: **1** (0.3 mmol), **2a** (0.2 mmol), Na₂CO₃ (1.5 eq.) and **E** (5 mol%) in 1 mL of CH₂Cl₂ and 0.5 mL of H₂O at 4 °C. Isolated yield after column chromatography. Determined by HPLC using chiral stationary phase. ^a 1 mmol reaction scale.

The absolute configuration of the stereogenic centre in compound **3ab** was determined to be (*S*) on the basis of X-ray crystallographic analysis (Figure 2); the configurations of the rest of the products **3** were assigned on the assumption of a uniform mechanistic pathway.¹⁷

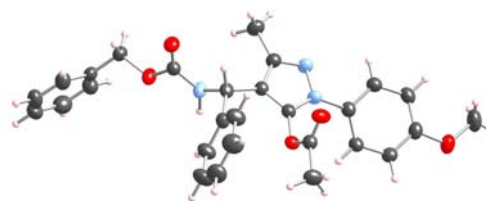
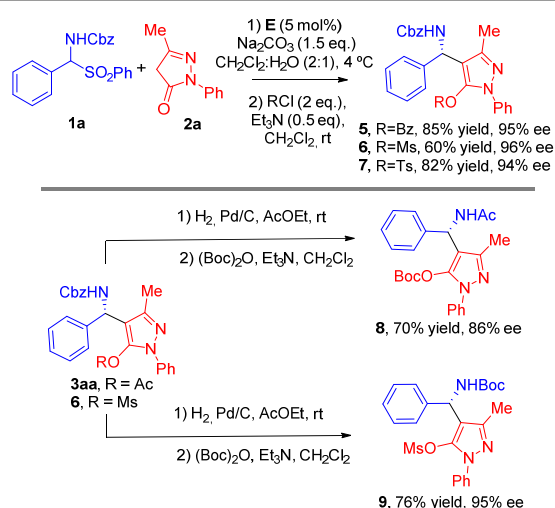


Figure 2 X-ray structure of **3ab**.

Once we studied several α -amido sulfones and different substituted pyrazolones, we turned our attention to the trapping agent for the enol form of the pyrazolone moiety (Scheme 4). After the addition of **2a** to the α -amido sulfone **1a** was completed, benzoyl chloride (BzCl) and Et₃N were added to the reaction mixture, and the corresponding chiral pyrazole **5** was obtained with excellent yield (85%) and enantioselectivity (95% ee). Similarly, when mesyl chloride (MsCl) or tosyl chloride (TsCl) were used for the second step, the corresponding mesylated pyrazole **6** and tosylated pyrazolone **7** were obtained with good yields and excellent enantiomeric excesses. Finally, the deprotection of Cbz group of adduct **3aa** was performed in the presence of H₂ and Pd/C (Scheme 4). However, we could not isolate the free amine, and we decided to protect *in situ* with (Boc)₂O in order to facilitate the isolation. Interestingly, the product obtained presented the structure **8**, which come from the transacetylation and protection of the enol form with (Boc)₂O. In this reaction a slightly erosion of the enantiomeric excess was observed. We also attempted the deprotection of the mesylated pyrazole **6** in the presence of H₂ and Pd/C, followed by an *in situ* protection of the free amine with (Boc)₂O. In this case, the Boc protected amine **9** was isolated with good yield (76%) and without loss of the enantiomeric purity.



Scheme 4. Evaluation of other protecting groups of the enol form of pyrazolone and deprotection of Cbz group.

Conclusions

In summary, we have described an organocatalytic asymmetric aminoalkylation of pyrazolones with aldimines generated *in situ* from α -amido sulfones using a quinine-derived squaramide organocatalyst, obtaining the corresponding chiral amines bearing a pyrazole moiety with good yields (up to 98%) and excellent enantioselectivities (up to 99% ee) under mild reaction conditions. Furthermore, the enol form of the pyrazolone product could be trapped with different agents as Ac₂O, BzCl, MsCl or TsCl. Studies to further extend the scope of this reaction are currently underway in our laboratory.

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- 17 CCDC 1944351 (**3ab**) 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.