DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Organocatalytic Enantioselective Alkylation of Pyrazol-3-ones with Isatin-Derived Ketimines: Stereocontrolled Construction of Vicinal Tetrasubstituted Stereocenters

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Quinine derived thiourea catalysed the enantioselective addition of 4-substituted pyrazolones to isatin-derived ketimines, providing a variety of amino oxindole-pyrazolone adducts containing congested vicinal tetrasubstituted stereocenters with excellent outcomes (up to 98% yield, >20:1 dr and 98% ee).

Keywords: asymmetric catalysis; ; pyrazolones ; isatin-derived ketimines; organocatalysis; quaternary stereocenters

The catalytic enantioselective synthesis of building blocks with contiguous quaternary stereocenters is a hot topic because of the prevalence of such structural motifs in natural and bioactive compounds.[1] This goal represents one of the greatest challenges in organic synthesis, due to the steric congestion making difficult the selective C-C bond formation.[2] In this context, the efficient assembly of multifunctionalised heterocyclic compounds containing quaternary stereocenters is of great importance. For example, the 3-substituted 3-amino-2-oxindole[3] skeleton bearing a tetra-substituted stereogenic center at the 3-position is a privileged heterocyclic structure present in many biologically active natural products and pharmaceutical drugs (SSR149415,[4] AG-041R[5] or NITD609[6]). The addition of nucleophiles to isatin-derived ketimines is one of the most straightforward methodology established for synthesis of chiral 3-substituted 3-amino-2-oxindole.[3b,7] However, only few succesful examples have been described for the assembly of vicinal tetrasubstituted stereogenic centers using isatin-derived ketimines as electrophiles.[8] On the other hand, the pyrazolone is a prominent heterocycle,[9] which exists in plenty of biologically active coumpounds with antiinflamatory, antiviral, antitumor or antibacterial properties;[10] moreover, pyrazol-3-ones are present in numerous pharmaceutical compounds (edaravone,[11] metamizole[12] or remogliflozin etabonate[13]). Despite the importance of pyrazolone derivatives, the examples of the synthesis of optically pure 4,4-disubstituted-3-pyrazolones are scarce.[14,15] Very recently Yuan,[15a] Feng,[15b-d] Rios[15e-f] and Gong[15g] described the enantioselective additions of 4-substituted pyrazolone derivatives to different electrophiles, for the synthesis of pyrazolone bearing a chiral quaternary stereocenter. However, the addition of 4-substituted pyrazolone derivatives to ketimines has not been described.[16]

Herein, we wish to report the addition of 4-substituted pyrazolones to isatin-derived ketimines using a bifunctional organocatalyst, leading to chiral heterocyclic compounds containing both amino oxindole and pyrazolone moieties bearing vicinal quaternary stereocenters with good yields and excellent diastereo- and enantioselectivity (Figure 1).

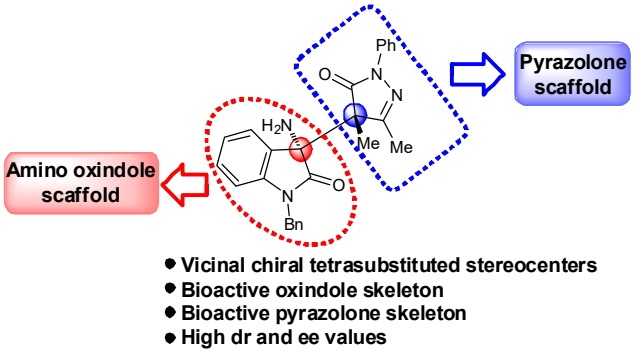
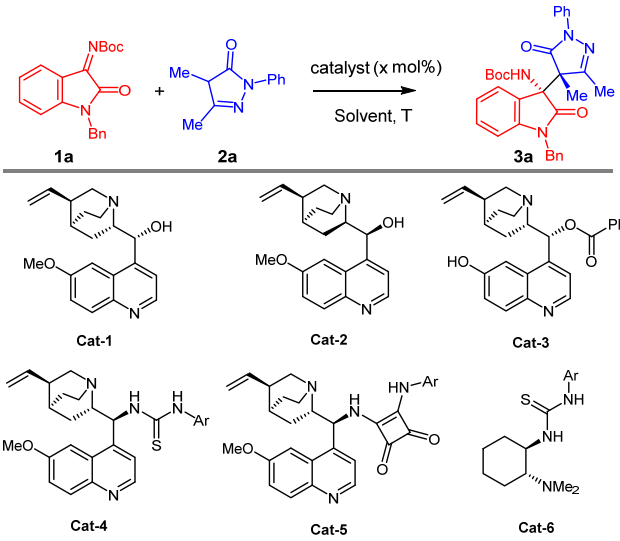


Figure 1. Construction of vicinal tetrasubstituted stereogenic centers in the addition of pyrazol-3-ones to isatin-derived ketimines.

Our initial studies were focused on the addition of 4,5-dimethyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (**2a**) to isatin-derived *N*-Boc ketimine **1a** in the presence of a series of bifunctional organocatalysts.[17]

Table 1. Optimization of the reaction conditions.[a]

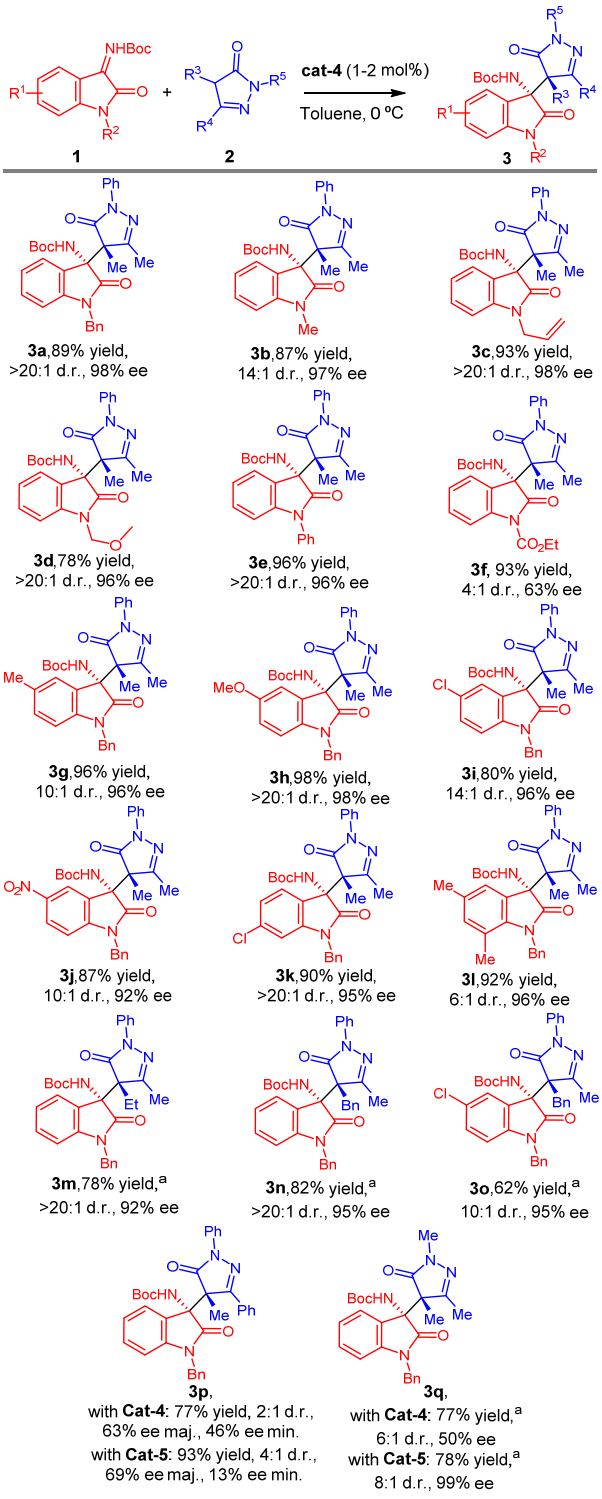


Entry	Catal. (mol%)	t(h)	Conv. (%)[b]	d. r.[b]	ee maj (%)[c]	ee min (%)[c]
1	**Cat-1** (5 %)	2	Full	5:1	18	9
2	**Cat-2** (5 %)	2	98	6:1	66[d]	15[d]
3	**Cat-3** (5 %)	1	Full	2:1	27	49[d]
4	**Cat-4** (5 %)	1	Full	>20:1	96	n.d.
5	**Cat-5** (5 %)	1	Full	>20:1	95	n. d.
6	**Cat-6** (5 %)	1	Full	4:1	91[d]	63[d]
7[e]	**Cat-4** (5 %)	2	Full	8:1	84	18
8[f]	**Cat-4** (5 %)	2	Full	18:1	96	n. d.
9	**Cat-4** (2 %)	1,5	Full	17:1	95	n. d.
10	**Cat-4** (1 %)	1,5	Full	17:1	96	n. d.
11[g]	**Cat-4** (1 %)	1,5	Full	>20:1	98	n. d.

[a] **1a** (0.05 mmol), **2a** (0.051 mmol) and catalyst (x mol%) in 1 mL of toluene at rt. [b] Determined by ^{1}H NMR. [c] Determined by HPLC using chiral stationary phase. [d] Opposite enantiomer was obtained. [e] CH_2Cl_2 was used as solvent. [f] Et_2O was used as solvent. [g] The reaction was performed at 0 ºC. Ar=3,5-$(CF_3)_2$-C_6H_3.

As shown in Table 1, when 5 mol% of quinine (**Cat-1**) was used in toluene, full conversion was obtained within 2 hours, providing compound **3a** in 5:1 diastereomeric ratio (d.r.) and poor enantiomeric excesses for both diastereoisomers (entry 1). Quinidine (**Cat-2**) afforded **3a** with better d.r. (6:1), and enantiomeric excesses (66% ee for the major diastereoisomer, entry 2). Cupreine derivative **Cat-3**, could catalyse the reaction but product **3a** was obtained with poor diastereo- and enantioselectivities (entry 3). Quinine derived thiourea **Cat-4** and quinine derived squaramide **Cat-5**, exhibited excellent reactivity with high stereocontrol, giving full conversion to product **3a** with excellent d.r. (>20:1) and high enantiomeric excess (96% ee with **Cat-4** and 95% ee with **Cat-5**, entries 4 and 5 respectively). With commercially available Takemoto's catalyst (**Cat-6**) a decreased in the diastereoselectivity was observed (4:1 d. r.; entry 6). Different solvents were tested with **Cat-4**, achieving lower selectivities (entries 7 and 8). A reduction in the catalyst loading was then investigated (entries 9 and 10), observing similar enantioselectivities but slightly lower diasteroisomeric ratios. Finally, by using 1 mol% of **Cat-4** in toluene at 0 °C (entry 11), product **3a** was gained with excellent stereoselectivity (>20:1 dr and 98% ee).

Having established the optimal reaction conditions (entry 11, Table 1) that are similar to the reported in the work of Wennemers for the addition of monothiomalonate to isatin-ketimines,[8c] the scope of the reaction was evaluated (Scheme 1). First, *N*-substitution of oxindole nitrogen was investigated (Scheme 1, **3a-3f**). Groups such as benzyl, methyl, allyl, methoxymethyl or phenyl were well tolerated, and the corresponding products were obtained with high diastereo- and excellent enantioselectivities. However, when the nitrogen was protected with an ethoxycarbonyl group, the corresponding product **3f** was obtained with lower diastereo- and enantioselectivity. Meanwhile when a tosyl protecting group was used, very poor reactivity and diastereoselectivity was observed and the products were obtained as a nearly racemic mixtures. Next, the effect of substitution in the benzene ring of the *N*-benzyl protected isatin ketimines was studied (**3g-3l**). Different electron-donating (Me or MeO) or electron-withdrawing (Cl or NO_2), were tolerated at the 5 position of the isatin-derived ketimine, affording the corresponding products with good yields and high stereocontrol. Moreover, ketimines with substituents at 6 or 7 positions reacted smoothly, providing the tertiary amines **3** with good results. Next, the substrate scope with respect to 4-substituted pyrazolones (ethyl or benzyl) was evaluated (**3m-3o**) obtaining good values of diastereo- and enantioselectivity, although a decrease in the reactivity was observed. When 4-methyl-2,5-diphenyl-pyrazolone was used as a nucleophile, poor d.r. and ee values were observed (**3p**) with **Cat-4**, although the diastereoselectivity could be increased with quinine derived squaramide (**Cat-5**). Finally, the reaction with 2,4,5-trimethyl-pyrazolone, gave compound **3q** with a good d.r. and moderate enantioselectivity. Nevertheless, when **Cat-5** was used, the product **3q** was afforded with better d.r. (8:1) and excellent enantioselectivity (99% ee).



Scheme 1. Scope of the addition of pyrazolones to isatin derived *N*-Boc ketimines: **1** (0.05 mmol), **2** (0.051 mmol) and **Cat-4** (1 mol%) in 1 mL of toluene at 0 °C. Isolated yields after column chromatography. Diastereoselectivities were determined by ^{1}H NMR of the crude reaction mixture. Enantioselectivities of the major diastereoisomer were determined by HPLC using chiral stationary phase. [a)] 2 mol% of catalyst was used.

The absolute configuration of the two stereogenic centers in compound **3i** was determined to be (*3R, 4'S*) on the basis of X-ray crystallographic analysis (Figure 2); the configuration of the rest of the products **3** was assigned on the assumption of a uniform mechanistic pathway.[18].

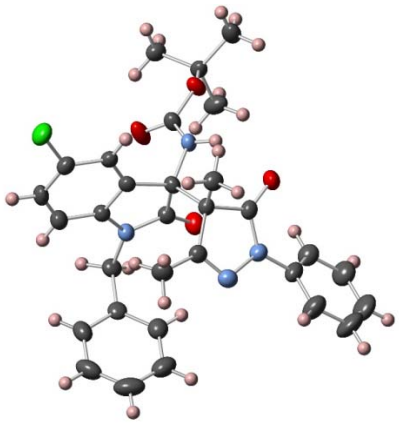
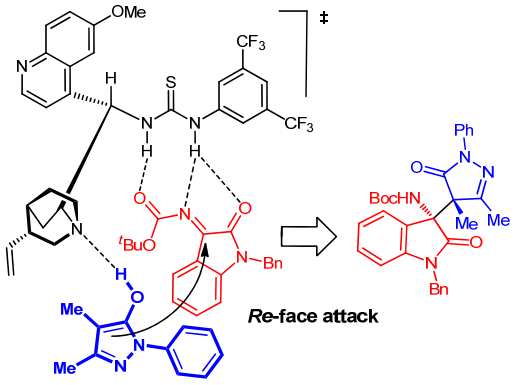


Figure 2. X-ray crystal structure of **3i**.

A plausible transition-state model is depicted in Scheme 2. The thiourea acts as bifunctional organocatalyst responsible for the preorientation and the activation of the substrates. While the isatin derived *N*-Boc ketimine moiety is activated upon formation of hydrogen bonds between the *N*-Boc group and the thiourea, the pyrazolone undergoes nucleophilic activation by hydrogen bonding with the quinuclidine moiety of the catalyst.[19] The 4-substituted pyrazolone will be directed to the *Re*-face of the ketimine, thus accounting for the observed enantioselectivity.



Scheme 2. Plausible transition-state model.

In summary, we have described the enantioselective amino alkylation of 4-substituted pyrazolones with isatin-derived *N*-Boc ketimines catalysed by quinine derived thiourea organocatalysts. This approach provides a new methodology to synthesize optically active compounds containing vicinal tetrasubstituted stereocenters. The reaction shows a wide substrate scope for different *N*-Boc imines and 4-substituted pyrazolones. The present study extends the scope of the catalytic asymmetric amino alkylation with isatin

derived ketimines, providing a new class of amino oxindole derivatives.[3] Studies to further extend the scope of this reaction and evaluation of the biological activities of compounds **3** are currently underway in our laboratory.

Experimental Section

General Procedure

A test tube containing ketimine **1** (0.1 mmol), pyrazolone **2** (0.1 mmol) and thiourea **Cat-4** (0.6 mg, 0.001 mmol) was purged with N_2. Then, 1.0 mL of toluene was added and the mixture stirred at 0 ºC until the reaction was complete (TLC). Finally, the reaction mixture was directly poured to the column chromatograpy, using hexane:EtOAc (95:5) as eluent to afford product **3**.

Acknowledgements

Financial support from the MINECO (Gobierno de España and FEDER (EU)) (CTQ2013-47949-P) and from Generalitat Valenciana (ISIC2012/001) is gratefully acknowledged. C. V. thanks MINECO for JdC contract. Access to NMR, MS and X-ray facilities from the Servei central de support a la investigació experimental (SCSIE)-UV is also acknowledged.

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Organocatalytic Enantioselective Alkylation of Pyrazol-3-ones with Isatin-Derived Ketimines: Stereocontrolled Construction of Vicinal Tetrasubstituted Stereocenters

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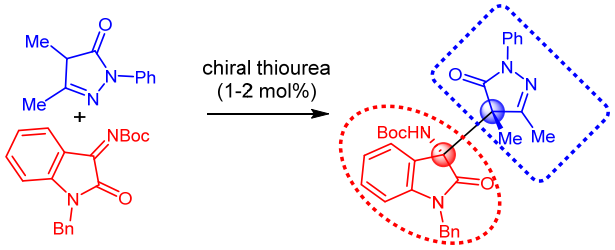

- **Vicinal chiral tetrasubstituted stereocenters**
- **Bioactive oxindole skeleton**
- **Bioactive pyrazolone skeleton**
- **High dr and ee values**