FULL PAPER

DOI: 10.1002/chem.200((……))

Amination of Pyrazolones: Scope and Limitations

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**Abstract:** The organocatalytic amination of pyrazol-5-ones with azodicarboxylates (catalyzed by quinine) is reported. This asymmetric process furnishes enantiomerically enriched hydrazine adducts containing quaternary stereocenters in high yields (74-96%) and enantioselectivities (up to ee 97%). Theoretical calculations allow us to propose the relations between quinine catalyst and reactants leading to observed stereochemical outcome and trends in effectivity of the reaction.

**Keywords:** (amination · azodicarboxylate · organocatalysis · pyrazolones · quinine)

Introduction

In the last two decades, the development of new organocatalytic reactions has been emerged as one of the most promising fields in organic chemistry for the synthesis of enantiopure compounds. Since the early works of List and MacMillan regarding intermolecular aldol1 and Diels-Alder reaction,2 the quest to expand activation modes, substrate scope, and more green processes have rendered thousands of notable works that generated what is commonly known as the Golden Age of Organocatalysis.

Heterocycles have always been an area of interest due to their presence in biologically active compounds. In our research group, we become interested in heterocycles that in earlier 2008 were almost unused in organocatalyzed methodologies despite their importance: Pyrazolones.3

Pyrazolones are nitrogen-containing five-membered heterocyclic compounds with widespread applications as pharmaceutical and agrochemical agents, synthetic scaffolds in combinatorial and medicinal chemistry, dyes4 or as chelating agents. Noteworthy, numerous pyrazolone derivatives were approved by FDA, such as antipyrine (**A**) firstly synthesized by Knorr, aminophenazone (**B**) with antipyretic and anti-inflammatory activities or eltrombopag (**C**) used for the treatment of low blood platelet counts in adults with idiopathic chronic immune thrombocytopenia (Figure 1).5



Figure 1. Selected examples of biologically relevant compounds.

Moreover, at that time (2008) none organocatalytic methodologies were developed for their enantioselective synthesis.6 For this reason, we started a vigorous research program towards the development of organocatalytic methodologies leading to the enantioselective synthesis of these privileged structures.7

The first example of enantioselective organocatalyzed reactions using pyrazolone derivatives was reported by Zhao in 2009.8 They described cupreine-catalyzed a domino Michael/Thorpe-Ziegler process between pyrazolones and benzylidene malononitriles affording 6-amino-5-cyanodihydropyrano[2,3-c]-pyrazoles with excellent enantioselectivity. Soon after, in 2010, we published our first example of an enantioselective methodology for the synthesis of pyrazolones, few months before Yuan and coworkers reported the first enantioselective pyrazolone addition to nitrostyrenes with moderate stereoselectivities using thiourea catalysts.9 Our work was dealing with the synthesis of a variety of spiro compounds, including pyrazolone motif. The reaction consists of the addition of pyrazolone to enal catalyzed by chiral secondary amines. The reaction occurs via a double Michael addition followed by intramolecular aldol reaction and dehydration to furnish the spiro compound.10,7b

Later, inspired by the previous work of Feng using gadolinium catalysts,11 we studied the amination of pyrazolones using cinchona alkaloids as catalysts.12 The reaction between pyrazolones and azodicarboxylates renders the final products in good yields and reasonable to excellent enantioselectivities.

In recent years, other groups devoted their efforts to the development of new asymmetric methodologies using pyrazolones; Enders, Wang, Lattanzi, Lu, Xu and many others achieved high levels of stereocontrol and high reactivity.13

Since the pioneering works on the α-amination of aldehydes reported by List and Jorgensen in 2002,14 α-amination of carbonyls with azodicarboxylates has been one of the most common strategies for the enantioselective C-N bond formation.15 In this full paper we describe the scope and limitations of the amination of Pyrazolones using diazoacetates as a Nitrogen source.

Results and Discussion

 In our previous short report about organocatalyzed α-amination of pyrazolones,12 several 4-aryl and 4-alkyl substituted pyrazolone derivatives were subjected to the reaction with azodicarboxylates to afford the corresponding enantiomerically enriched adducts. After optimization steps, quinine was identified as a suitable catalyst in the reaction conditions indicated below. However, the lack of a deeper study on the effects of the interactions between the organocatalyst and the reactants does not allow us to appoint some general trends in relation to the stereoselective outcome and yield of the reaction.

In the beginning, we set out experiments to examine the reactivity of various 4-benzyl pyrazolones. The results are summarized in Table 1. Both electron-withdrawing (EWG) and electron-donating groups (EDG) on the benzyl substituent were tolerated affording corresponding adducts **3** in very high yields and good to excellent enantioselectivities. First, we ran the reaction with 4-nitrobenzyl derivative to prove the reproducibility of the method. As expected, 4-(4-nitrobenzyl) pyrazolone afforded the adduct **3ba** in 74% yield and good enantioselectivity (*ee* 72%, entry 2), which is in agreement with the previous report (yield 72%, *ee* 70%).12 When using 4‑substituted 4-benzyl pyrazolones carrying EDG, a similar reaction efficiency was observed as in the case of unsubstituted 4-benzyl pyrazolone (**3aa**). For example, 4‑methylbenzyl and 4‑methoxybenzyl derivatives produced the corresponding adducts **3ea** and **3ha** in slightly higher yields with increased enantioselectivity (entry 5, 8), respectively. The substituted benzyl group at 3-position, as exemplified with 3-methylbenzyl pyrazolone, showed similar efficiency and level of enantioselectivity (*ee* 85%, entry 6). Conversely, the presence of 3-nitrobenzyl group led to a large drop in the enantioselectivity of the reaction (*ee* 58%, entry 3). This observed deterioration of enantiocontrol could be caused by preferential H-bonding between nitro group and the organocatalyst. Luckily, changing the organocatalyst to cinchonidine rendered **3ba** and **3ca** with much better enantioselectivity. Gratifyingly, when 4-benzyl pyrazolones with the substituents attached at 2-position were used, the reactions took place smoothly with excellent levels of enantioselectivity (*ee* 88-97%) and good yields (83-86%). In addition, 4-substituted pyrazolones carrying a heteroaromatic ring (**3ia-3ka**) also provide satisfactory results. Slightly higher yields and optical purity of the adducts were observed in the case of more electron-rich thiophene-bearing derivatives (**3ja**‑**ka**).

Table 1. Screening of various 4-substituted pyrazolone derivatives in organocatalytic reaction.



Then, we explored the effects of various groups at other positions located on the pyrazolone ring (Table 2). Interestingly, when switching the 3-methyl to 3-ethyl group of pyrazolone, reaction furnished product **3la** in excellent yield and very high enantioselectivity (*ee* 93%, entry 2). Hence, similar substrate, 4-allyl- 3-ethyl pyrazolone, was also tested in the reaction. Disappointingly, the corresponding adduct **3ma** was obtained only with moderate yield and stereoselectivity. Next, the introduction of the larger phenyl groups at both 3- and 4-positions on pyrazolone ring led to almost complete disruption of an asymmetric induction of the studied transformation. Nevertheless, product **3na** was isolated in high yield (89%, entry 4). When the same sterically demanding substrate **1n** was subjected to the reaction with less bulky diethylazodicarboxylate (DEAD), a remarkable increase of stereoinduction of the process was observed (*ee* 24% vs. 90%, entries 4 and 5).

After that, we turn our attention to bicyclic pyrazolone derivatives **1o** and **1p**. The amination reaction of **1o** with DIAD gave the desired product in nearly quantitative yield 95% with excellent enantioselectivity (ee 95%, entry 6). However, a similar substrate carrying the tetraline fragment (**1p**) showed only modest reactivity in terms of yield and enantioselectivity (78%, ee 72%). A significant decrease of enantioselectivity was also observed when electron-withdrawing 2,4-dinitrophenyl group was introduced on amide nitrogen of pyrazolone ring (entry 8). In addition, we tested an effect of sterically demanding *tert*-butyl group present on pyrazolone substrate, unfortunately, the amination process proceeded with low enantiocontrol.

Table 2. Screening of variously substituted pyrazolone derivatives in organocatalytic reaction.



The inexpensive starting materials and catalyst used predetermine this amination procedure for scale-up preparations. As shown in Scheme 2, the gram scale experiment was performed successfully, albeit with slight erosion of reaction efficiency to the experiments reported previously (92%, *ee* 84%, ref.12 vs. 72%, *ee* 74%). Besides the known deprotection procedure of hydrazine derivatives **3**,12 we tested another transformation valuable for enhanced structural diversity of the enantiomerically enriched pyrazolones prepared. 4-Allyl derivative **3ma** was employed in a metathesis reaction with styrene using 2nd generation Hoveyda-Grubbs catalyst, and the corresponding product **5ma** was obtained as a pure *E*-isomer in high yield 77% without change of optical purity (Scheme 2).

An absolute configuration of pyrazolone derivatives **3** was determined as *R* by comparing the data with known compounds from the literature.11,12



Scheme 2. Further transformations of pyrazolone adducts.

To understand the origin of the stereoselectivity of this reaction, we have investigated the stereoselectivity-determining step of the reaction using the density functional theory (DFT) methods.16 The quinine catalyzed amination of pyrazolones may follow the catalytic cycle shown in the scheme 1. It involves deprotonation of pyrazolone, addition of pyrazolone to azodicarboxylate (C – N bond formation step), and proton transfer from the catalyst to the adduct. Since chirality induction or inversion is not possible in the proton abstraction and transfer step *i.e* in the first and last step of the reaction, addition of pyrazolone to azodicarboxylate (C – N bond formation step) is expected to be the stereoselectivity-determining step of the reaction. Transition states for different possible conformers of reactants and catalyst, which lead to (*R*) and (*S*)-products, were located at the M062X/6-31G\* level of theory.17 The lowest energy diastereomeric transition states **TS-(*R*)** and **TS-(*S*)** were considered for further analysis. Relative to separated reactants and catalyst, the free energies of transition states **TS-(*R*)** and **TS-(*S*)** are 4.7 and 7.8 kcal/mol, respectively. The difference in free energies corresponds to enantiomeric excess (ee) of 99% in favor of the *R*–product, which is in reasonable agreement with the experimentally observed stereochemical outcome of the reaction.

Having established the stereo-controlling transition states, we sought to identify the factor that creates the stereo-differentiation between TS-(*R*) and TS-(*S*). The optimized geometries for the transition states of addition step (C – N bond formation) are shown in Figure 1. It is noticed that both these transition states (TS-(*R*) and TS-(*S*)) are stabilized via multiple non-covalent interactions. Four major interactions which involve hydrogen bonding interactions between (catalyst)NH∙∙∙∙N(azodicarboxylate), (catalyst)NH∙∙∙∙O(pyrazolone), (catalyst)OH∙∙∙∙O(azodicarboxylate), and (catalyst)OH∙∙∙∙O(pyrazolone) are identified. Inspection of optimized geometries of transition states clearly shows that lowest energy transition state TS-(*R*) enjoys a larger number of stabilizing interactions comparing to the TS-(*S*).



**TS-(*R*) TS-(*S*)**

**Figure 1**. Optimized transition states for the addition step. The values in parentheses indicate Select bond distances are given in Å and corresponding electron densities at the bond critical path is given in the parentheses. Atom colors: H = white, C = Silver, N= blue, O = red.

To corroborate the presence of these hydrogen bonding interactions, we have analyzed the topology features of electron density distribution at transition states using multiwfn program.18 The distances of hydrogen bonding interactions and corresponding electron densities at the BCP are provided in Figure1. The electron densities of bond critical points (BCPs) for hydrogen bonding interactions are found to be in the range of 0.011 to 0.038 *au* which typically indicate moderate non-covalent interactions. The strength of hydrogen bonding interactions as suggested by electron densities of bond critical points for these interactions at the TS-(*R*) are slightly weaker compared to the hydrogen bonding interactions found in TS-(*S*). However, the network of hydrogen bonding interactions at the TS-(*R*) can effectively stabilize the developing charges in both the substrates (pyrazolone as well as azodicarboxylate) rather than the couple of strong hydrogen bonding interactions at the TS-(*S*). The difference in the stabilizing interactions at the transition states is also reflected in the catalyst–substrates interaction energies (E*int*) of TS-(*R*) and TS-(*S*).19 The E*int*between catalyst and substrates at the TS-(*R*) is found to be 11.5 kcal/mol higher than the TS-(*S*). Hence, we reasoned that subtle differences in the hydrogen bonding interactions offered by the catalyst at the diastereomeric transition states might be responsible for the energy difference between TS-(*R*) and TS-(*S*).

Conclusion

In summary, we succesfully presented enantioselective amination of pyrazol-5-ones with azodicarboxylates catalyzed by *Cinchona* alkaloids. The reaction showed a wide substrate scope for variously decorated pyrazol-5-ones. The method provided optically active compounds containing quaternary stereocenter with very high yields and enatioselectivities using readily available materials with no additional requirements.

The computational investigations of the quinine catalyzed amination of pyrazolone revealed a crucial role of the catalyst (quinine) in stereo-selectivity determining step wherein, the catalyst interacts with both the substrates via multiple hydrogen bonds. These interactions allow effective stabilization of developing charge on the substrates in the transition state. Furthermore, computational model has shown that the different degrees of hydrogen bonding interactions offered by the catalyst in the competing transition states determine the stereochemical outcome of the reaction.

Experimental Section

*General amination procedure of pyrazolones* ***3***

Substituted pyrazol-5-one **1** (0.1 mmol, 1.0 equiv.) and quinine (0.01 mmol, 0.1 equiv.) were dissolved in toluene (2 mL) and stirred for 10 min at room temperature. The solution was cooled to –40 °C then azodicarboxylate **2** (0.2 mmol, 2.0 equiv.) was added. The reaction mixture was stirred at –40 °C until reaching full conversion (monitored by TLC, 2 d). Then the reaction mixture was directly loaded on a silica gel column. Column chromatography (hexanes/EtOAc: 7/1 → 3/1) furnished corresponding product **3**. The *ee* value of the product **3** was determined by HPLC analysis on a chiral stationary phase.

ASSOCIATED CONTENT

Supporting Information

Spectral data for all prepared compounds with copies of the 1H NMR, 13C NMR and HPLC chromatograms are available online from [http://xxxxxxxxxxx](http://xxxxxxxxxxx/).

Accession codes

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Notes
The authors declare no competing ﬁnancial interests.

Acknowledgements ((optional))

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Jan Veselý gratefully acknowledges the Czech Science Foundation (No 16-23597S) for the financial support. Bedřich Formánek thanks the Charles University Grant Agency (No 393615) for the financial support. We also thank Dr. Simona Petrželová for the NMR service provided, Dr. Martin Štícha for his MS analysis.

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

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