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Organocatalytic Amination of Pyrazolones with Azodicarboxylates: Scope and Limitations

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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 the effectivity of the reaction.

Introduction

Pyrazolones[1] are nitrogen-containing five-membered heterocyclic compounds with widespread applications as pharmaceutical and agrochemical agents, synthetic scaffolds in combinatorial and medicinal chemistry, dyes, and chelating agents.[2,3] Noteworthy, numerous pyrazolone derivatives were approved by FDA, such as antipyrine (**A**) firstly synthesized by Knorr,[4] 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]

Hence, new synthetic pathways for this class of heterocycles, especially in an asymmetric fashion, have been extensively explored. The pyrazolone structural motif, containing lactam bearing two adjacent nitrogen atoms, features many reactive sites, which can be utilized to get valuable derivatives. Interestingly, until 2008, no organocatalytic methods were developed for the enantioselective synthesis of functionalized pyrazolones.[6] For this reason, we started a vigorous research program developing organocatalytic strategies 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 a cupreine-catalyzed 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,[10,7b] few months before Yuan and coworkers reported the first enantioselective pyrazolone addition to nitrostyrenes using thiourea catalysts.[9] 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.

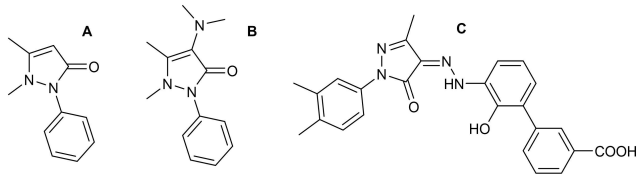

Figure 1. Selected examples of biologically relevant compounds.

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 azodicarboxylates 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

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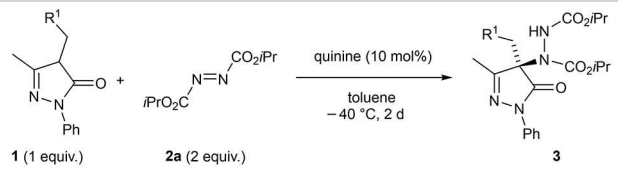
as a suitable catalyst in the reaction conditions indicated below. However, the lack of a deeper study on the effects of the interactions between the organocatalyst and the reactants does not allow us to appoint some general trends in relation to the stereoselective outcome and yield of the reaction.

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 **3 ba** 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 (**3 aa**). For example, 4-methylbenzyl and 4-methoxybenzyl derivatives produced the corresponding adducts **3 ea** and **3 ha** 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 **3 ba** and **3 ca** 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 (**3 ia**–**3 ka**) 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 (**3 ja**–**ka**).

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, the reaction furnished product **3 la** in excellent yield and very high enantioselectivity (*ee* 93%, entry 2). Hence, a similar substrate, 4-allyl-3-ethyl pyrazolone, was also tested in the reaction. Disappointingly, the corresponding adduct **3 ma** was obtained only with moderate yield and stereoselectivity. Next, the introduction of the larger phenyl groups at both 3- and 4-positions on the pyrazolone ring led to almost complete disruption of an asymmetric induction of the studied transformation. Nevertheless, product **3 na** was isolated in high yield (89%, entry 4). When the same sterically demanding substrate **1 n** was subjected to the reaction with less bulky diethyl azodicarboxylate (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 **1 o** and **1 p**. The amination reaction of **1 o** 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 (**1 p**) showed only modest reactivity in terms of yield and enantioselectivity (78%, *ee* 72%). A significant decrease of enantioselectivity was also observed when the electron-withdrawing 2,4-dinitrophenyl group was introduced on amide nitrogen of pyrazolone ring.

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

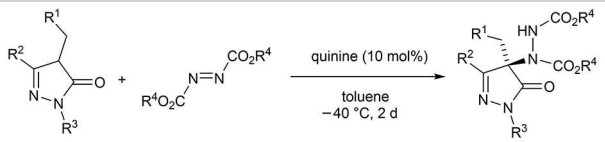


1 (1 equiv.) **2a** (2 equiv.) **3**

Entry	R^1	Product	Yield [%][a]	*ee* [%][b]
1	Ph	**3aa**	80	83
2	4-$NO_2C_6H_4$	**3ba**	74 (76)	72 (82)[c]
3	3-$NO_2C_6H_4$	**3ca**	79 (92)	58 (77)[c]
4	2-$NO_2C_6H_4$	**3da**	86	97
5	4-$CH_3C_6H_4$	**3ea**	81	79
6	3-$CH_3C_6H_4$	**3fa**	79	85
7	2-$CH_3C_6H_4$	**3ga**	83	88
8	4-$CH_3OC_6H_4$	**3ha**	87	83
9	2-furyl	**3ia**	87	74
10	2-thienyl	**3ja**	91	85
11	3-thienyl	**3ka**	90	79

[a] Isolated yield after column chromatography. [b] Ee determined by HPLC analysis. [c] For values in brackets, cinchonidine was used as a catalyst.

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



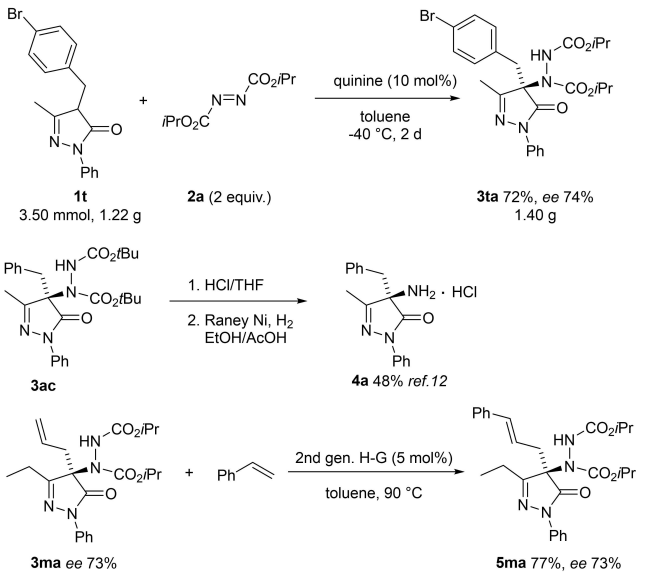
1 (1 equiv.) **2** (2 equiv.) **3**

Entry	R^1	R^2	R^3	R^4	Product	Yield [%][a]	*ee* [%][b]
1	Ph	Me	Ph	*i*Pr	**3aa**	80	83
2	Ph	Et	Ph	*i*Pr	**3la**	96	93
3	CH_2=CH-	Et	Ph	*i*Pr	**3ma**	79	73
4	Ph	Ph	Ph	*i*Pr	**3na**	89	24
5	Ph	Ph	Ph	Et	**3nb**	92	90
6			Ph	*i*Pr	**3oa**	95	95
7			Ph	*i*Pr	**3pa**	78	72
8	Ph	Me	2,4-$NO_2C_6H_3$	*i*Pr	**3qa**	80	65
9	Ph	Me	4-$CH_3OC_6H_4$	*i*Pr	**3ra**	93	89
10	Ph	Me	*t*Bu	*i*Pr	**3sa**	86	38

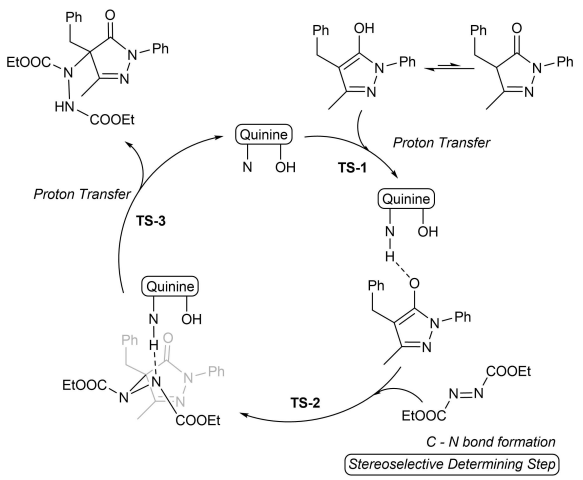
[a] Isolated yield after column chromatography. [b] *Ee* determined by HPLC analysis.

On the other hand, electron-rich substituents, such as OCH_3, had a positive impact on both yield and enantiomeric excess (entry 8 vs. 9). In addition, we tested an effect of sterically demanding *tert*-butyl group present on pyrazolone substrate; unfortunately, the amination process proceeded with low enantiocontrol.

The inexpensive starting materials and catalyst used predetermine this amination procedure for scale-up preparations. As shown in Scheme 1, the gram scale experiment was performed successfully, albeit with slight erosion of reaction efficiency to the experiments reported previously (92%, *ee* 84%,[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 **3 ma** was employed in a metathesis reaction with styrene



Scheme 1. Further transformations of pyrazolone adducts.



Scheme 2. Catalytic cycle of the pyrazolone amination.

using 2nd generation Hoveyda-Grubbs catalyst, and the corresponding product **5 ma** was obtained as a pure *E*-isomer in high yield 77% without change of optical purity (Scheme 1).

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

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 Scheme 2. It involves deprotonation of pyrazolone, the 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, the addition of pyrazolone to azodicarboxylate (C–N bond formation step) is expected to be the stereoselectivity-determining step of the reaction. Transition states for the addition of pyrazolone to azodicarboxylate were located at the M062X/6-31G* level of theory.[17] The optimized geometries of key transition states (**TS-(*R*)** and **TS-(*S*)**) are shown in Figure 2. The attack of *Re*-face of pyrazolone to azodicarboxylate *via* **TS-(*R*)** leads to the *'R'* product whereas the addition of *Si*-face of pyrazolone to azodicarboxylate via **TS-(*S*)** provides the *'S'* product. 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.

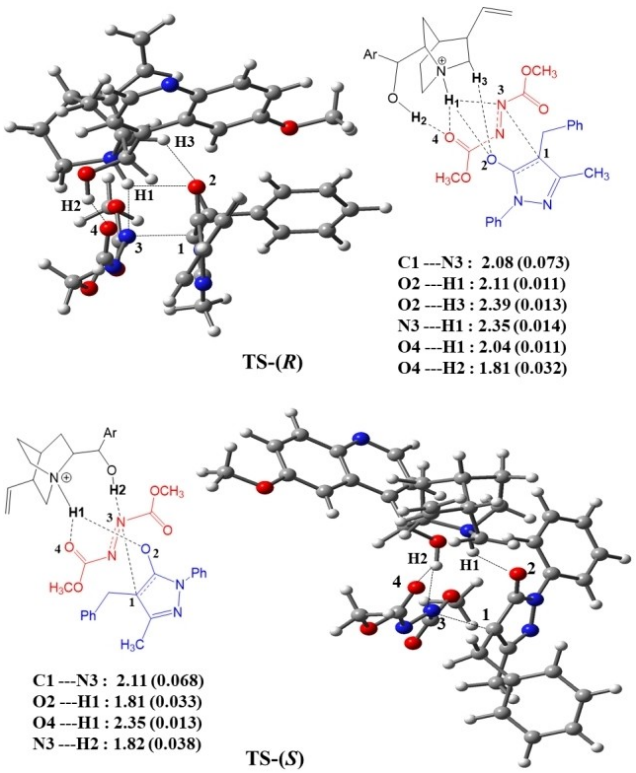


Figure 2. Optimized transition states of **TS-(*R*)** and **TS-(*S*)**. Select bond distances are given in Å and corresponding electron densities at the bond critical path is given in the parentheses. Atom colors: H = white, C = Silver, N = blue, O = red.

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 stereodifferentiation between **TS-(*R*)** and **TS-(*S*)**. It is noticed that both these transition states (**TS-(*R*)** and **TS-(*S*)**) are stabilized *via* multiple non-covalent interactions. Three major interactions, which involve hydrogen bonding interactions between (catalyst)NH····N(azodicarboxylate), (catalyst)NH····O(pyrazolone), and (catalyst)OH····O(azodicarboxylate) at the transition states, are identified. Besides these interactions, the pyrazolone and azodicarboxylate scaffolds enjoy additional stabilizing hydrogen bonding interactions in the **TS-(*R*)** (Figure 2).

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 Figure 2. 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 indicates 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 a 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 successfully presented the 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 enantioselectivities 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 the stereoselectivity 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, a 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 product **3** was determined by HPLC analysis on a chiral stationary phase.

Supporting Information (see footnote on the first page of this article): Spectral data for all prepared compounds with copies of the ^{1}H NMR, ^{13}C NMR, and HPLC chromatograms are available.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Amination · Organocatalysis · Nitrogen heterocycles · Synthetic methods

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