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Enantioselective organocatalytic amination of Pyrazolones

Michal Šimek,[a] Marek Remeš,[a] Jan Veselý*[a] and Ramon Rios*[b]

Pyrazolones[1] are common heterocycles present in several pharmacological active compounds like Metamizole, a powerful analgesic and antipyretic developed by Hoechst AG in 1920.
More recently, pyrazol-3-ones were found to be inhibitors of CD80, and to have potent activity in inhibiting protease-resistant prion protein accumulation, cytokines, p38 kinases and have been studied as multidrug resistance modulators.[2]

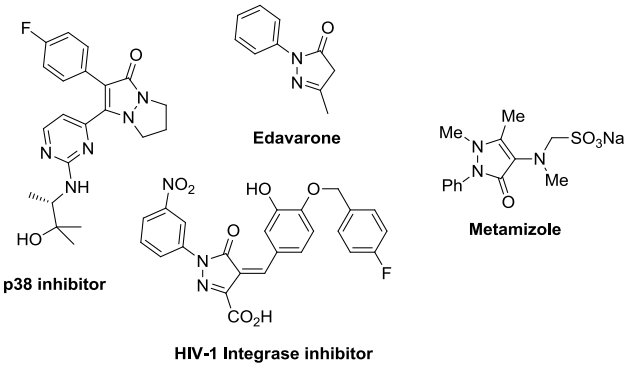
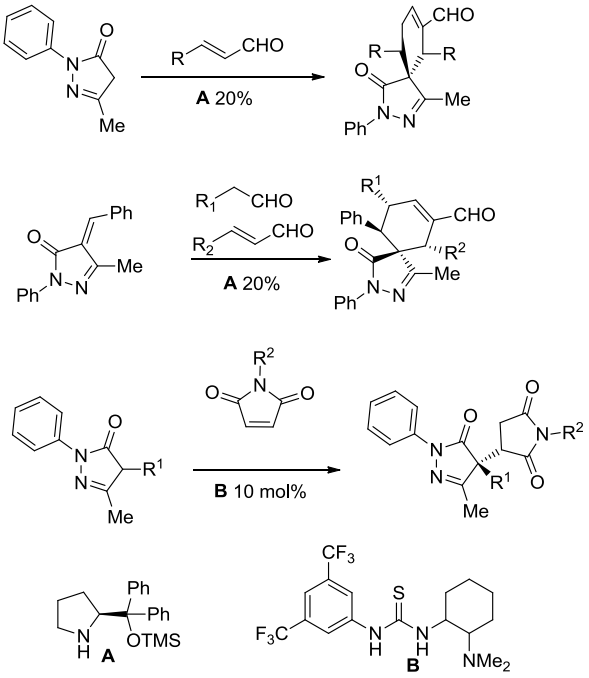


Figure 1. Biological active pyrazolones.

Despite the interest in pyrazolones as common structural motifs in pharmacologically active compounds, there are few methodologies that allow the construction of pyrazolones in asymmetric form. For example Yuan and co-workers described a highly enantioselective pyrazolone addition to nitrostyrenes catalyzed by thiourea compounds achieving the resulting chiral pyrazolones in high levels of enantio and diastereoselectivity.[3] Enlighted for the broad utility of pyrazolones, in our research group we have been developed several organocatalytic methodologies to give acces to different chiral pyrazolones. As it is shown in Scheme 1, we developed a synthesis for spiropyrazolones bearing 3 chiral centers via a Michael-Michael-Aldol sequence,[4] spirazolones bearing 4 asymmetric centers via a Michael-Michael-Aldol sequence,[5] and a enantioselective addition of pyrazolones to maleimides catalyzed by bifunctional thiourea-tertiary amine compounds. [6]
However, the organocatalytic direct addition of a heteroatom to the C-4 of the pyrazolone ring remains unexplored.



Scheme 1. Previous organocatalytic methodologies with pyrazol-3-one developed in our group.

Recently the α-amination of carbonyls with azodicarboxylates has been one of the most common strategies for the enantioselective C-N bond formation.[7] In the kingdom of organocatalysis, since the pioneering works on the α-amination of aldehydes reported by List and Jorgensen in 2002, several research groups have been

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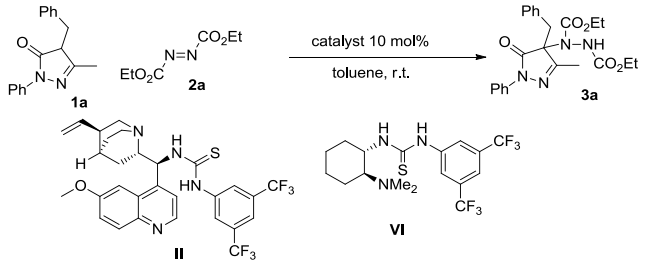
developing several α-aminations of ketoesters, ketones, oxindoles, and others.[8] For this reason, based on our previous experience in pyrazolone chemistry and organocatalysis[9] we turned our attention to the organocatalytic amination of pyrazolones. During the preparation of this manuscript, Feng and co-workers reported the organometallic version of the present reaction catalyzed by chiral Gd salts,[10] however it should be noted that our methodology presents some advantages like the non-use of metals, and the use of readily accessible and cheap catalysts such as quinine, instead of the *N,N'* dioxide ligand used by Feng.

To our delight, when pyrazolone **1a** was treated with azodicarboxylate **2a** in the presence of triethylamine, the reaction rendered the final compound with excellent yields (entry 1: table 1). Next, we decided to explore the enantioselective version of this reaction using as catalysts different chiral bases or bifunctional thiourea-tertiary amine catalysts (table 1). The best catalyst using toluene as the solvent at room temperature was quinine, that afforded the adduct **3a** in excellent conversions and with good enantioselectivity (74% ee, entry 5). Under the same conditions, cinchonidine (entry 2) had given inferior results. Other commercially available chiral bases such as Sharpless ligands (entries 6 and 10) or β-ICPD (entry 8) did not give satisfactory results. As expected, quinine- and quinidine-derived catalysts showed opposite senses of enantioselective induction (compare entries 2, 4, 5 and 9, for instance). Although bifunctional amine-thiourea catalysts such as *epi*-quinine- and *takemoto* thioureas (entries 3 and 7, respectively) showed catalytic activity, the stereoselectivity of the reaction was only moderate.

Table 1: Catalyst Screening[a]

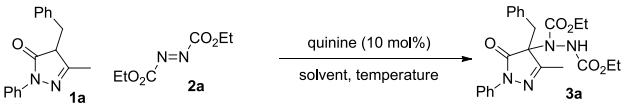


Entry	Catalyst	Conversion [c]	ee [d]
1	Et_3N	100% (90%)[e]	-
2	cinchonidine (**I**)	100%	65%
3	**II**	100%	45%
4	quinidine (**III**)	100%	-49%
5	quinine (**IV**)	100%	74%
6	$(DHQD)_2AQN$ (**V**)	100%	9%
7	**VI**	100%	31%
8	β-ICPD (**VII**)	100%	-15%
9	cinchonine (**VIII**)	100%	-42%
10	$(DHQD)_2PHAL$ (**IX**)	100%	15%

a) In a small vial, pyrazolone **1a** (0.30 mmol), diethyl azodicarboxylate **2a** (0.25 mmol) and the catalyst (0.025 mmol) were stirred in toluene (1 mL) for 14 h at the temperature specified in the Table. b) See Chart II for the structures of the catalysts. c) Determined by ^{1}H NMR analysis of the crude reaction. d) Enantiomeric excess of the major diastereomer, determined by chiral HPLC. e) Isolated yield after purification by column chromatography.

In order to increase the enantioselectivity of the reaction we studied the reaction behaviour at different temperatures and solvents in order to find the best conditions (table 2). The best conditions for the reactions were toluene as a solvent, at -40ºC that renders the final adduct **3a** in full conversion after 3 days and in 82% enantioselective excess.

Table 2: Conditions Screening[a]

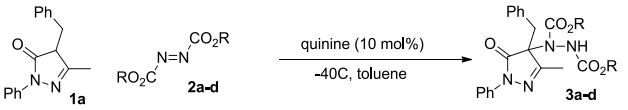


Entry	Solvent	Temp.	Conversion [b]	ee [c]
1	toluene	r.t.	100%	74%
2	DCM	r.t.	100%	42%
3	AcOEt	r.t.	100%	50%
4	MTBE	r.t.	100%	58%
5	MeOH	r.t.	100%	11%
6	DMF	r.t.	100%	7%
7	toluene	0C	100%	76%
8	toluene	-20C	100%	79%
9	toluene	-40C	100%	82%

a) In a small vial, pyrazolone **1a** (0.30 mmol), diethyl azodicarboxylate **2a** (0.25 mmol) and the catalyst (0.025 mmol) were stirred in toluene (1 mL) for 3 days at the temperature specified in the Table. b) Determined by ^{1}H NMR analysis of the reaction crude. c) Enantiomeric excess determined by chiral HPLC.

Next we studied the reaction of pyrazolone **1a** with different azodicarboxylates. As it is shown in table 3, the best results were obtained when diisopropyl azodicarboxylate was used affording the final compound in the optimized conditions in 82% yield and 84% ee. The use of bulkier azodicarboxylates such as ditertbutyl azodicaboxylate give slightly worse results in both terms of yield and enantioselectivity (entry 3).

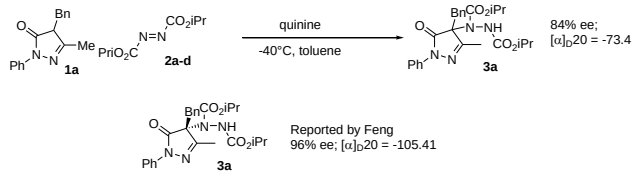
Table 3: Azodicarboxylate Scope[a]



Entry	R	3	Yield [b]	ee [c]
1	Et (**2a**)	**3a**	85%	82%
2	i-Pr (**2b**)	**3b**	82%	84%
3	t-Bu (**2c**)	**3c**	79%	82%
4	Bn (**2d**)	**3d**	55%	84%

a) In a small vial, pyrazolone **1a** (0.10mmol), azodicarboxylate **2a-d** (0.20 mmol) and quinine (0.020 mmol) were stirred in toluene (2 mL) for 2 days. b) Isolated yield after purification by column chromatography c) Enantiomeric excess determined by chiral HPLC.

In order to determine the absolute configuration of the final compounds we compared with the previous compounds reported by Feng. When the reaction was catalyzed by quinine the (*R*)-enantiomers were obtained.

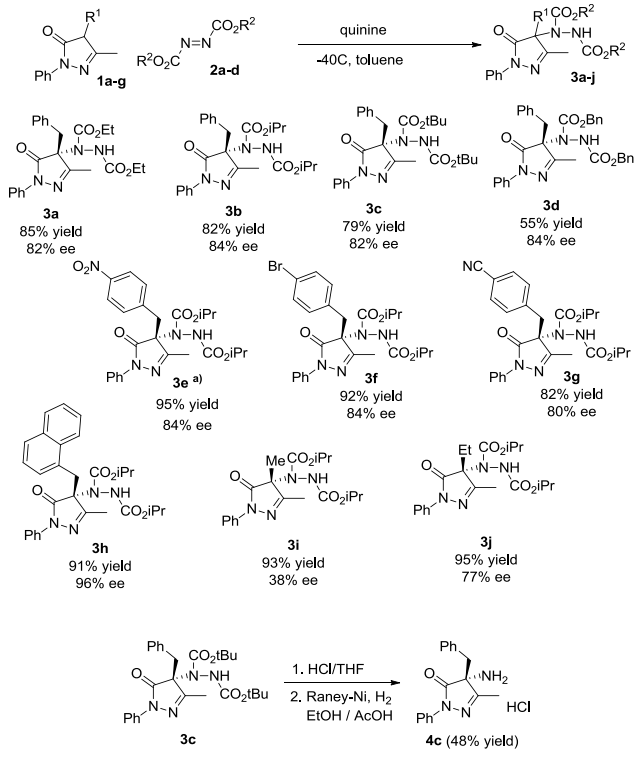


Scheme 2. Determination of absolute configuration.

Then, we shifted our attention to the pyrazolone moiety. As shown in Scheme 3, to our delight, DIAD **2b** reacted with a set of pyrazolones **1a-g** and successfully rendered the aminated products **3a-j** in good yields, and with variable enantioselectivities. When benzyl-derived pyrazolones were used, in all the examples good to excellent enantioselectivities were obtained. Interestingly, the presence of substituents at the *ortho*-position of the phenyl ring does not have a influence in the enantioselectivity of the reaction. For example, the 4-cyanophenyl derivative was obtained in 82% yield and 80% ee. Surprisingly the 4-nitro derivative was obtained in moderate yields and moderate enantioselectivities when quinine was used as catalyst (72% yield, 70% ee); however changing the catalyst to cinchonidine renders in the same conditions **3e** in 95% yield and 84% ee. The best results were obtained when naphtyl derivative pyrazolone as used giving **3h** in 91% yield and 96% ee.

When C4-alkyl pyrazolones were used the recation renders the corresponding aminate products **3i-j** with excellent yields and with good enantioselectivities in the case of the ethyl derived (**3j**), however when we use the methyl derived pyrazolone the enantioselectivity drops dramatically (38%ee, **3i**). Should be noticed that the reaction with alkyl derived pyrazolones is dramatically affected by the steric bulkiness of the alkyl group and the azodicarboxylate; when diethyldicarboxylate were used instead of diisopropyldiazodicarboxylate we obtained **3i** and **3j** in almost racemic form.

Furthermore, subsequent decarboxylation/reduction reaction sequence was also performed, affording corresponding optically active amines **4** in good yields with remained enantiomeric purity (Scheme 3).



Scheme 3. Scope of the reaction and subsequent decarboxylation/reduction. a) Reaction catalyzed with cinchonidine.

In summary we reported the first enantioselective organocatalytic amination of pyrazolones. The final aminated products were obtained in good yields and in good to excellent enantioselectivities. This methodology represents a nice alternative to the previously organometallic amination of pyrazolones reported by Feng and coworkers. The advantages of the present report consist in the use of inexpensive catalysts (cinchona alkaloids) and without the use of such as Gd salts with complex ligands reported previously.

Experimental Section

General procedure for the amination of pyrazol-5-one derivatives (**3**): Substitued pyrazol-5-one **1** (1.0 equiv., 0.1 mmol) and quinine (0.1 equiv., 0.01 mmol) was dissolved in toluene (2 mL) and stirred for 10 minutes. The mixture was cooled down at -40 °C and azodicarboxylate **2** (2.0 equiv., 0.2 mmol) was added. The reaction was stirred at the temperature -40 °C for 48h. The crude product was purified by column chromatography (gradient n-hexane/EtOAc 5:1 to 3:1) on silicagel. The enantiomeric excess of the product **3** was determined by chiral HPLC analysis (Chiralpak IC column).

(*R*)-diisopropyl 1-(4-benzyl-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)hydrazine-1,2-dicarboxylate (**3b**): brown solid, 82% yield; 84% ee; $[\alpha]_D$= -73.4 (c = 0.98 in $CHCl_3$); HPLC (Chiralpak IC column), hexane/i-PrOH = 96/4, flow rate 1.0 mL/min. ^{1}H NMR (300MHz $CDCl_3$): δ = 7.45 (d, J=7.5Hz, 2H), 2.29 – 7.22 (m, 1H), 7.15 – 7.06 (m, 7H), 5.05 (hept, J=7.5Hz, 1H), 4.90 (hept, J=7.5Hz, 1H), 3.35 (d, J=12.6Hz, 1H), 3.07 (d, J=12.6Hz, 1H), 2.38 (s, 3H), 1.34 (t, J=4.2Hz, 6H), 1.17 – 1.11 (m, 6H) ppm. ^{13}C NMR (150,91 MHz $CDCl_3$): δ 171.9, 159.7, 156.8, 153.6, 137.2, 131.1, 129.7 (2C), 128.4 (2C), 128.1 (2C), 127.7, 125.1, 119.3, 73.5, 71.8, 70.4, 38.7, 29.6, 22.0, 21.8, 21.7, 21.7, 14.0 ppm. IR (KBr): ν = 3282, 3060, 3031, 2977, 2929, 2872, 2851, 1712, 1595, 1503, 1455, 1377, 1314, 1248, 1177, 1108, 761 cm^{-1}. ESI-HRMS: calcd for $C_{25}H_{31}O_5N_4^+$ ($[M + H]^+$).

(*R*)-diisopropyl 1-(4-naphth-1-ylmethyl-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)hydrazine-1,2-dicarboxylate (**3h**): brown solid, 91% yield, 96% ee; $[\alpha]_D$= -104,4° (c = 0,45 in $CHCl_3$); HPLC (Chiralpak IC column), hexane/*i*-PrOH = 90/10 flow rate 1.0 mL/min. ^{1}H NMR (300MHz $CDCl_3$): δ 8,12 (d, *J*=8.4Hz, 1H), δ 7,70 (d, *J*=7.2Hz, 1H), 7,60 (d, *J*=8.1Hz, 1H), 7,48-7,30 (m, 3H), 7,25-7.16 (m, 1H), 7,19-7,10 (m, 5H), 6,99-6,97 (m, 1H), 5,13 (hept, *J*=6.3Hz, 1H), 4,91 (hept, *J*=6.3Hz, 1H), 3,89 (d, *J*=13.2, 1H), 3,64 (d, *J*=13.2Hz, 1H), 2,30 (s, 3H), 1,34-1,32 (m, 6H), 1,13-1,06 (m, 6H) ppm. ^{13}C NMR (150,91 MHz $CDCl_3$): δ 172.5, 160.3, 157.0, 153.7, 136.9, 133.6, 132.0, 128.7, 128.6, 128.3 (2C), 127.4, 125.7, 125.5, 124.9, 124.6, 123.5, 119.1, 73.4, 71.8, 70.5, 34.0, 31.8, 29.3, 22.0, 21.8, 21.7, 21.6, 14.7 ppm. IR (KBr): *ν* = 3294, 3060, 3043, 2983, 2941, 2878, 1736, 1715, 1595, 1503, 1452, 1371, 1320, 1245, 1180, 1111, 785, cm^{-1}. ESI-HRMS: calcd for $C_{29}H_{33}O_5N_4$ ($[M + H]^+$) 517.2446, found 517.2446.

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Keywords: oraganocatalysis • amination • pyrazolone • enantioselective • cinchona alkaloids

[1] For an excellent book about the chemistry of pyrazol-3-ones: Pyrazol-3-ones. Part IV: *Synthesis and Applications. G. Varvounis. Adv. Heterocyclic Chem.* Katritzky, A. R. (Ed.); Academic Press Inc **2009**, 98, 143..

[2] a) Y. L. Janin, *Bioorg. Med. Chem*. **2007**, 15, 2479; b) M. T. Gutierrez-Lugo, C. J. Bewley, *Med. Chem*. **2008**, 51, 2606; c) I. R.Matthews, PCT Int.Appl. WO 46679(2005); d) A. Kimata, H. Nakagawa, R.Ohyama, T. Fukuuchi, S. Ohta, T. Suzuki, N. Miyata, *J. Med. Chem.* **2007**, 50, 5053.

[3] Y.-H. Liao, W.-B. Chen, Z.-J. Wu, X.-L. Du, L.-F. Cun, X.-M. Zhang, W.-C. Yuan, *Adv. Synth. Catal.* **2010**, 352, 827.

[4] A.-N. R. Alba, A. Zea, G. Valero. T. Calbet, M. Font-bardia, A. Mazzanti, A. Moyano, R. Rios, *Eur. J. Org. Chem.* **2011**, 1318.

[5] A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano, R. Rios, *Org. Biomol. Chem*. **2011**, *9*, 6519-6523.

[6] A. Mazzanti, T. Calbet, M. Font-Bardia, A. Moyano, R. Rios, *Organic & Biomolecular Chemistry* **2012**, 10, 1645-1652.

[7] For reviews on asymmetric α-amination reactions, see: a) L.-W.Xu, J. Luo, Y. Lu, Chem. Commun. **2009**, 1807. b) C. Najera, J. M. Sansano, *Chem. Rev*. **2007**, 107, 4584. (c) J. M. Janey, *Angew. Chem.,Int. Ed*. **2005**, 44, 4292; d) G. Gallina, D. J. Ramon, *Tetrahedron: Asymmetry* **2006**, 1465. e) C. Greck, B. Drouillat, C. Thomassigny, *Eur. J. Org. Chem* **2004**, 1377; f) T. Vilaivan, W. Bhanthumnavin, *Molecules* **2010**, 15, 917. For selected examples of asymmetric α-amination, see: g) T. Bui, G. Hernandez-Torres, C. Milite, C. F. Barbas III. *Org. Lett*. **2010**, 12,5696. h) X. Han, F. Zhong, Y. Lu, Y. *Adv. Synth. Catal*. **2010**, 352, 778.i) S. Mouri, Z. Chen, H. Mitsunuma, M. Furutachi, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc*. **2010**, 132, 1255. j) Z. G. Yang, Z. Wang, S. Bai, K. Shen, D. H. Chen, X. H. Liu, L. L. Lin, X. M. Feng, *Chem.Eur. J*. **2010**, 16, 6632. k) T. Bui, M. Borregan, C. F. Barbas, III. *J. Org.Chem*. **2009**, 74, 8935. l) T. Mashiko, N. Kumagai, M. Shibasaki, *J. Am.Chem*. Soc. **2009**, 131, 14990. m) R. He, X. Wang, T. Hashimoto, K. Maruoka, *Angew. Chem., Int. Ed.* **2008**, 47, 9466. n) T.-Y. Liu, H.L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett*. **2007**,9, 3671. m) T. Mashiko, K. Hara, D. Tanaka, Y. Fujiwara, N. Kumagai, M. Shibasaki, *J. Am. Chem. Soc*. **2007**, 129, 11342.

[8] For selected examples see: a) F. Zhou, M. Ding, Y.-L. Liu, C.-H. Wang, C.-B. Ji, Y.-Y. Zhang, J. Zhou, Adv. Synth. Catal. **2011**, 353, 2945; b) N. Kurumagurubaran, K. Juhl, W. Zhuang, A. Bøgevig, K.A. Jørgensen, *J. Am. Chem. Soc*. **2002**, 124, 6254; c) L. Cheng, L. Liu, D. Wang, D., Y.-J. Che, Org. Lett. **2009**, 6, 3874: d) T. Bui, T., M. Borrego, C. F., Barbas III, J. Org. Chem. **2009**, 74, 8935; e) B. List, *J. Am. Chem. Soc*. **2002**,*124*, 5656; f) A. DEsmanchelier, H. Yalgin, V. Coeffard, X. Moreau, C. Greck, *Tetrahedron Lett.* **2011**, *52*, 4430; g) J.-Y. Fu, Q.-C. Yang, Q.-L. Wang, J.-N. Ming, F.-Y. Wang, X.-Y. Xu, L.-X. *J. Org. Chem*. **2011**, *76*, 4661; h) C. Liu, Q. Zhu, K.-W. Huang, Y. Lu, *Org. Lett*. **2011**, *13*, 2638.

[9] For a non exhaustive list of our previous works in organocatalysis see: a) G. Valero, A.-N. Balaguer, A. Moyano, R. Rios, *Tetrahedron Lett*. **2008**, 49, 6559; b) X. Companyó, G. Valero, L. Crovetto, A. Moyano, R. Rios, *Chem. Eur. J*. **2009**, 15, 6564; c) X. Companyó, M. Hejnová, M. Kamlar, J. Veselý, A. Moyano, R. Rios, *Tetrahedron Lett*. **2009**, 50, 5021; d) X. Companyó, A.-N. Balaguer, F. Cárdenas, A. Moyano, R. Rios, *Eur. J. Org. Chem*. **2009**, 3075; e) A.-N. R. Alba, X. Companyó, G. Valero, A. Moyano, R. Rios, *Chem. Eur. J*. **2010**, 16, 5354; f) X. Companyó, A. Zea, A.-N. R. Alba, A. Mazzanti, A. Moyano, R. Rios. *Chem. Commun.* **2010**, 46, 6953; g) G. Valero, J. Schimer, I. Císařová, J. Veselý, A. Moyano, R. Rios, *Tetrahedron Lett*. **2009**, 50, 1943; h) S. Číhalová, G. Valero, J. Schimer, M. Humpl, M. Dračínský, A. Moyano, R. Rios, J. Veselý, *Tetrahedron* **2011**, 67, 8942-8950; i) M. Remeš, J. Veselý *Eur. J. Org. Chem*. **2012**, 3747-3752.

[10] a) Z. Yang, Z. Wang, S. Bai, X. Liu, L. Lin, X. Feng, *Org. Lett*. **2011**, 13, 596-599. For similar pyrazolone additions catalyzed by N-oxide metal complexes see: b) Z. Wang, Z. Chen, S. Bai, W. Li, X. Liu, L. Lin, X. Feng, *Angew. Chem., Int. Ed*. **2012**, 51, 2776-2779; c) Z. Wang, Z. Yang, D. Chen, X. Liu, L. Lin, X. Feng, *Angew. Chem., Int. Ed*. **2011**, 50, 4928-4932. For an excellent review: d) X. Liu, L. Lin, X. Feng, *Acc. Chem. Res*. **2011**, 44, 574-587.

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Layout 2:

Organocatalytic amination

Michal Šimek, Marek Remeš, Jan Veselý and Ramon Rios**

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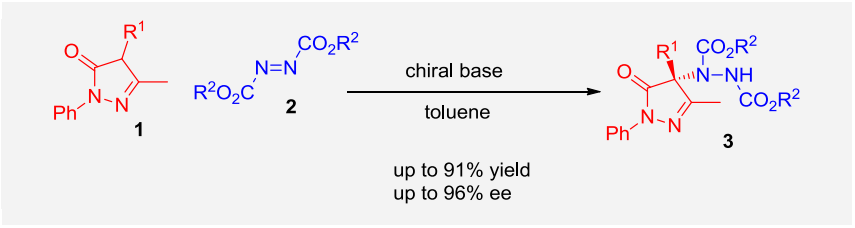

The first organocatalytic enantioselective amination of pyrazolones is reported. The reaction between pyrazolones and diazodicarboxylates is simple catalysed by quinine affording the final amino pyarazolone derivatives in excellent yields and good enantioselectivities.