Regio-, Diastereo-, and Enantioselective Organocatalytic Addition of 4-Substituted Pyrazolones to Isatin-Derived Nitroalkenes

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Abstract: Hydroquinine 2,5-diphenyl-4,6-pyrimidinediyl diether [(DHQ)$_2$Pyr] catalyzed the regio-, diastereo-, and enantioselective addition of 4-substituted pyrazolones to isatin-derived nitroalkenes, providing a variety of chiral alkenylpyrazolone adducts containing a tetrasubstituted stereocenter bearing an oxindole moiety with excellent yields, regioselectivity, and diastereoselectivity, as well as a moderate enantioselectivity (up to 98 % yield, > 20:1 *E*/*Z* ratio *dr* and 78 % *ee*). The reaction harnesses a nitroalkene as an alkenylating agent through a Nucleophilic Vinylic Substitution (S_NV) reaction.

Introduction

Pyrazolones are an important class of nitrogen heterocycles that have shown a broad range of biological activities and have attracted the attention of the pharmaceutical industry and medicinal chemistry.[1] This scaffold is present in a large variety of synthetic compounds that exhibit pharmaceuticals properties, such as antipyretic, analgesic, neuroprotective, antibacterial, etc.[2] In view of the great importance of the pyrazolone skeleton, the asymmetric synthesis of pyrazolones bearing a quaternary stereocenter have become an attractive goal and many and efficient synthetic approaches have been established over the last years.[3] So, several asymmetric additions of 4-substituted-pyrazol-3-ones to different electrophiles have been reported employing organo- and metal-catalysts for the synthesis of chiral pyrazolones bearing a tetrasubstituted stereocenter at 4 position, particularly when the substituent at this position is an alkyl group.[4] Nevertheless, the examples in the literature of enantioselective synthesis of chiral 4-alkenyl-4-substituted-pyrazolones are scarce.[5,6] Feng an co-workers,[5] in 2012, described a *Z*-selective asymmetric 1,4-addition reaction of 4-substituted pyrazolones to alkynones catalyzed by an *N*,*N*-dioxide-scandium(III) complex obtaining 4-alkenyl-4-substituted-pyrazolones with high geometric control, high yields, and excellent enantioselectivities (Figure 1). In view of the limited examples described, the development of other methodologies for the synthesis of chiral 4-alkenyl-4-substituted-pyrazolones is the great interest for organic synthesis.

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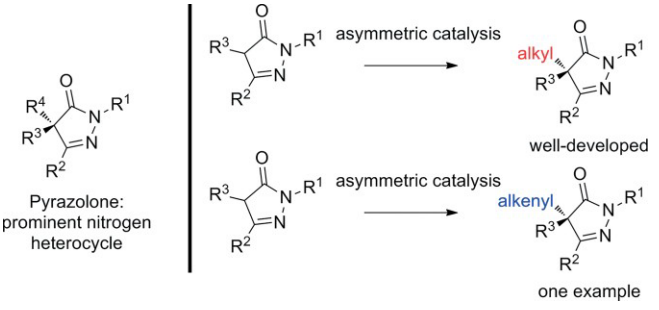
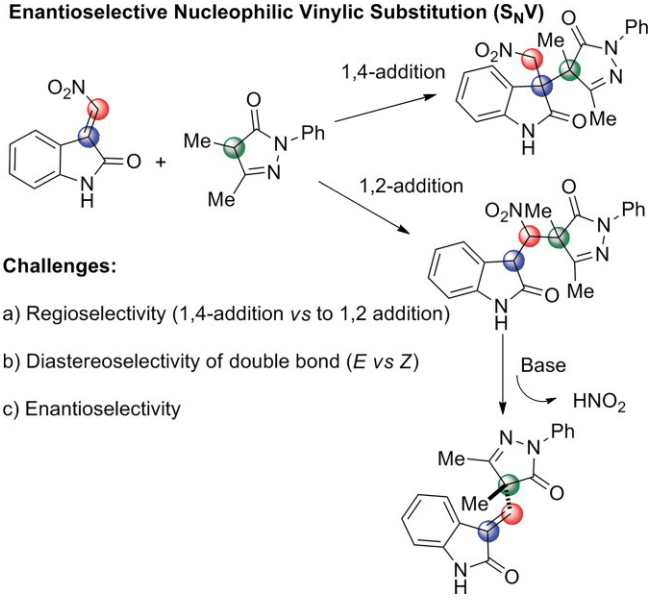


Figure 1. Enantioselective synthesis of chiral pyrazolones bearing a quaternary stereocenter at the 4-position.

On the other hand, 2-oxindole scaffold represents one of the most important structures for medicinal and pharmaceutical chemistry, due to the plenty of natural products and synthetic compounds bearing this motif that present biological activities.[7] As an important 2-oxindole structure, unsymmetrical 3-alkylideneoxindoles[8] are present in various natural products[9] and pharmaceutical drugs.[10] We envisioned that the synthesis of chiral pyrazolones bearing a 3-alkylideneoxindoles could be achieved by nucleophilic vinylic substitution (S_NV)[11] of 4-substituted-pyrazolones and (*E*)-3-(nitromethylene)indolin-2-one[12] (Scheme 1). However, the nucleophilic vinylic substitution in isatin-derived nitroalkenes have been scarcely studied.[13] Such transformation presents three challenges: the regioselectivity of the nucleophilic addition (attack at the **?**-position of the nitroalkene or at the *α*-position), the stereoselectivity of the 1,2-elimination and the enantioselectivity of the reaction. We have recently described a stereoselective addition of pyrazolones to isatin-derived nitroolefins in a racemic form.[14] As a part of our ongoing interest in the asymmetric addition of pyrazolones,[15] herein, we wish to report the addition of 4-substituted pyrazolones to isatin-derived nitroalkenes using a (DHQ)$_2$Pyr as an organocatalyst through a nucleophilic vinylic substitution (S_NV),

leading to chiral heterocyclic compounds containing both 3-alkylidene-2-oxindole and pyrazolone moieties bearing a fully carbon tetrasubstituted stereocenter with good yields, excellent regio- and diastereoselectivity and moderate enantioselectivity (Scheme 1).

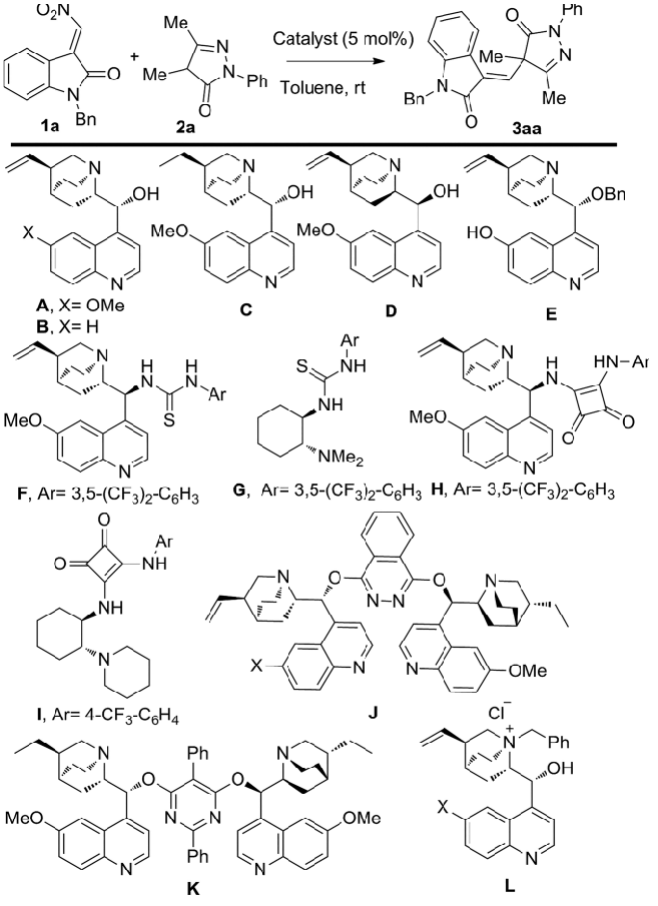


Scheme 1. Asymmetric synthesis of chiral pyrazolones bearing a 3-alkylidene-2-oxindole scaffold.

Results and Discussion

We initiated our studies by evaluating the nucleophilic addition of 4,5-dimethyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one **2a** to (*E*)-1-benzyl-3-(nitromethylene)indolin-2-one (**1a**) with various bifunctional organocatalysts (5 mol-%) in toluene at room temperature (Table 1). To our delight, quinine **A** could catalyze the reaction and the product **3aa** was obtained with 72 % yield, after 4 hours, with a poor 2:1 *E*/*Z* ratio, but with a promising 70 % ee (entry 1, Table 1). When cinchonidine **B** was used as catalyst similar results were obtained although with lower enantioselectivity (47 % ee, entry 2). While product **3aa** was obtained with lower *E*/*Z* ratio with hydroquinine **C** (entry 3) and with lower enantiomeric excess (59 % ee, entry 4) with quinidine **D**. Cupreine derivative **E** showed higher *E*/*Z* ratio(4:1), but the product **3aa** was obtained with lower enantioselectivity (41 % ee). When quinine-derived thiourea **F** was used, the reaction proceeds with lower enantioselectivity, however the Takemoto's thiourea **G** (entry 7) afforded product **3aa** with a good diastereomeric ratio of 7:1 and 52 % ee. Next different chiral squaramides were evaluated as catalysts (entries 8 and 9), showing that when quinine-derived squaramide **H** was used, the oxindole **3aa** was obtained with excellent *E*/*Z* ratio (14:1) and 50 % ee. Catalyst $(DHQ)_2PHAL$ **J** (entry 10) and $(DHQ)_2Pyr$ **K** (entry 11), were also tested in the S_NV reaction, obtaining similar *E*/*Z* ratio than catalyst **H**, but slightly better enantioselectivities (53 and 54 % ee, respectively). Finally, the ammonium salt **L**, gave practically pure the *E* isomer but with very low enantioselectivity (entry 12). Although quinine **A** gave better enantioselectivity (70 % ee) than $(DHQ)_2Pyr$ **K** (54 % ee), catalyst **K** gave the best *E*/*Z* ratio (16:1), while the diastereomeric ratio in the case of the quinine was very poor (2:1). In view of these results, we decided to choose catalyst **K** to continue further optimization by testing different solvents (Table 2).[16]

Table 1. Optimization of the catalyst.

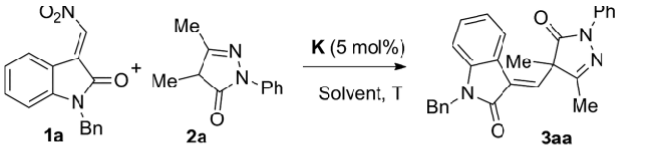


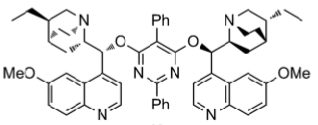
Entry[a]	Catalyst (5 mol-%)	*t* [h]	Yield [%][b]	*E*/*Z* ratio[c]	ee of the *E* isomer [%][d]
1	**A**	4	72	2:1	70
2	**B**	5	70	2.2:1	47
3	**C**	6	69	1.1:1	69
4	**D**	4	73	2.3:1	59[e]
5	**E**	5	62	4:1	41[e]
6	**F**	5	55	3:1	31
7	**G**	3	53	7:1	52[e]
8	**H**	5	71	14:1	50
9	**I**	5	54	4:1	33[e]
10	**J**	7	50	12:1	53
11	**K**	5	72	16:1	54
12	**L**	8	78	> 20:1	10

[a] Reaction conditions: 0.05 mmol **1a**, 0.1 mmol **2a** and catalyst (5 mol-%) in toluene (1 mL) at r.t. [b] Isolated yield after column chromatography. [c] *E*/*Z* ratio determined by ^1H NMR of the crude reaction mixture. [d] Enantiomeric excess determined by chiral HPLC. [e] Opposite enantiomer.

Therefore, a wide survey of solvents was tested for the S_NV reaction between **1a** and **2a** using 5 mol-% of catalyst **K**. First, different aromatic solvents such toluene, benzene, *o*-xylene,

Table 2. Optimization of the solvent in the S_NV reaction.





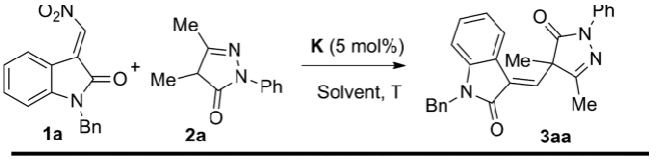
Entry[a]	Solvent	*t* [h]	Yield [%][b]	*E*/*Z* ratio[c]	ee of the *E* isomer [%][d]
1	toluene	5	72	16:1	54
2	**benzene**	**7**	**80**	**16:1**	**54**
3	*p*-xylene	5	63	12:1	59
4	*o*-xylene	5	69	15:1	58
5	$PhCF_3$	2	65	15:1	56
6	CH_2Cl_2	24	62	9:1	28
7	$CHCl_3$	24	65	10:1	40
8	Et_2O	2	78	8:1	25
9	THF	1	86	8:1	23
10	dioxane	1	97	20:1	33
11	**MTBE**	**5**	**98**	**> 20:1**	**64**
12	EtOAc	5	92	15:1	56
13	CH_3CN	5	62	13:1	2
14	*i*PrOH	24	77	8:1	15

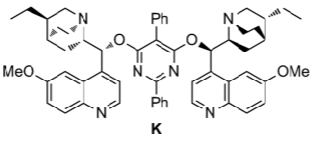
[a] Reaction conditions: 0.05 mmol **1a**, 0.1 mmol **2a** and catalyst (5 mol-%) in solvent (1 mL) at r.t. [b] Isolated yield after column chromatography. [c] *E*/*Z* ratio determined by ^{1}H NMR of the crude reaction mixture. [d] Enantiomeric excess determined by chiral HPLC.

p-xylene, and (trifluoromethyl)benzene were evaluated obtaining product **3aa** with high *E*/*Z* ratio and good enantiomeric excess, being the best solvent benzene (80 % yield, 16:1 *E*/*Z* ratio, 66 % ee, entry 2). Chlorinated solvents such CH_2Cl_2 and $CHCl_3$ were less efficient (entries 6 and 7, respectively). Also ethereal solvents such Et_2O, THF and dioxane gave bad results in terms of enantioselectivity. However, when MTBE was used as a solvent (entry 11, Table 2) an excellent 98 % yield, excellent > 20:1 *E*/*Z* ratio and 64 % ee was obtained. Other polar solvents such EtOAc or CH_3CN and protic solvents such as *i*PrOH, gave poor results. In view of these results, we decided to choose benzene and MTBE as solvents to further study of the optimization of the reaction conditions.

Next, we evaluated the catalyst loading used in the asymmetric S_NV reaction (Table 3). When a catalyst loading of 10 mol-% was used, lower enantioselectivity was obtained (entry 2), while when 2 mol-% of catalyst was used lower yield of compound **3aa** was achieved, observing similar enantioselectivity (entries 3). We also observed a decrease in the enantioselectivity of the reaction when MTBE was used as solvent (entries 5 and 6). Moreover, the concentration of the reaction mixture was evaluated (entries 7 and 8), observing lower enantioselectivities. At this point, we decided to study mixtures of benzene/MTBE as solvent to perform the reaction (entries 9 and 10). When 1 mL of a mixture benzene/MTBE (0.7:0.3) was used, the corresponding product **3aa** was obtained with 97 % yield, excellent > 20:1 *E*/*Z* ratio and the best enantioselectivity (68 % ee). Finally, by lowering the reaction temperature to 4 °C (entry 11), the enantioselectivity decreased to 64 % ee.

Table 3. Optimization of the reaction conditions.



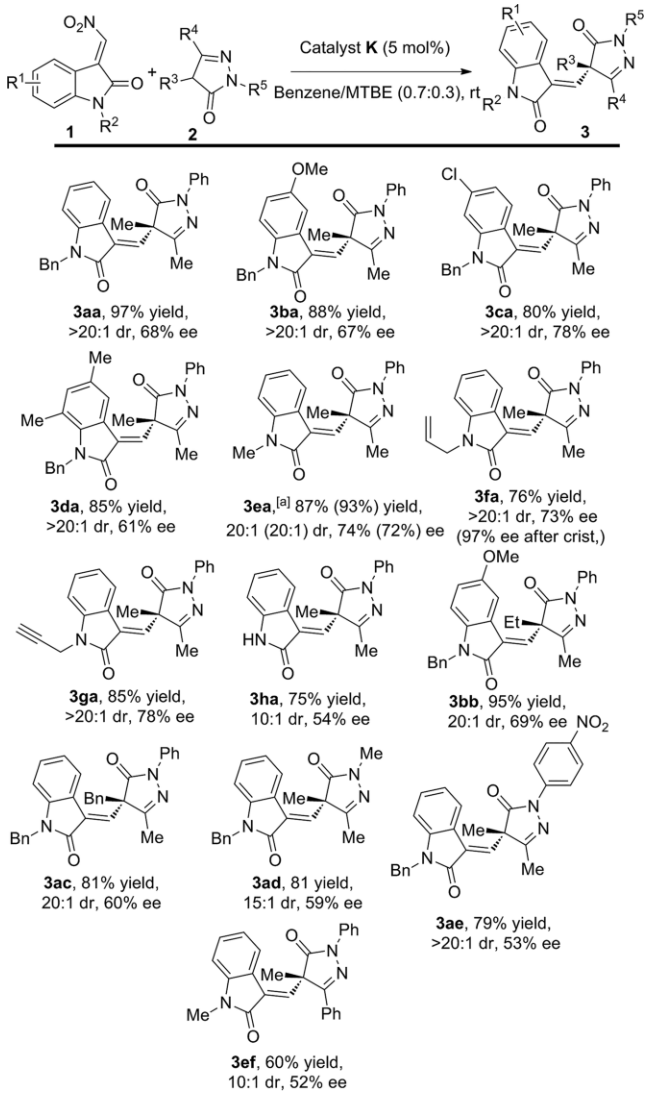


Entry[a]	Solvent	*t* [h]	Yield [%][b]	*E*/*Z* ratio[c]	ee of the *E* isomer [%][d]
1	benzene	7	80	16:1	66
2[e]	benzene	2	88	16:1	57
3[f]	benzene	6	67	16:1	65
4	MTBE	5	98	> 20:1	64
5[e]	MTBE	1	90	> 20:1	48
6[f]	MTBE	7	78	20:1	50
7[g]	benzene	2	81	15:1	58
8[h]	benzene	7	90	17:1	55
9	benzene/MTBE (1:1)	1	88	> 20:1	64
10	benzene/MTBE (0.7:0.3)	1	97	> 20:1	68
11[i]	benzene/MTBE (0.7:0.3)	7	63	> 20:1	64

[a] Reaction conditions: 0.05 mmol **1a**, 0.1 mmol **2a** and catalyst (5 mol-%) in solvent (1 mL) at r.t. [b] Isolated yield after column chromatography. [c] *E*/*Z* ratio determined by ^{1}H NMR of the crude reaction mixture. [d] Enantiomeric excess determined by chiral HPLC. [e] 10 mol-% of catalyst **K** was used. [f] 2.5 mol-% of catalyst **K** was used. [g] 2 mL of benzene was used. [h] 0.5 mL of benzene was used. [i] The reaction was performed at 4 °C.

With the optimized reaction conditions in hand (entry 10, Table 3), we proceeded to study the scope of the enantioselective addition of pyrazolones **2** to isatin-derived nitroalkenes **1** through a S_NV reaction (Scheme 2). Electron-donating (MeO, Me) or electron-withdrawing (Cl), were tolerated at the 5, 6 or 7 position of the isatin-derived nitroalkene, affording the corresponding products (**3ba**–**3da**) with good yields, excellent *E*/*Z* ratios and good enantiomeric excesses (up to 78 % ee). Next, the *N*-substitution of the oxindole nitrogen was evaluated (**3ea**–**3ia**). Groups such as methyl, allyl and propargyl were well accommodated, obtaining the corresponding 3-alkylidene-2-oxindoles **3** with better enantioselectivities (up to 78 % ee). Non-protected NH on the oxindole ring was also tolerated (**3ha**), although with lower yield, diastereoselectivity (10:1 *E*/*Z* ratio) and enantioselectivity (54 % ee). Different pyrazolones **2** were also evaluated in the reaction with nitroalkenes **1**. The reaction proceeded efficiently with high yields and excellent diastereoselectivity, although with lower enantioselectivity (53–69 % ee).

The configuration of the double bond in compound **3fa** was determined as *E* and the absolute configuration of the stereogenic center was determined to be (*S*) on the basis of X-ray crystallographic analysis (Figure 2); the configuration of the rest of the products **3** were assigned on the assumption of a uniform mechanistic pathway.[17]



Scheme 2. Scope of the enantioselective addition of 4-substituted-pyrazolones to isatin-derived nitroalkenes. Reaction conditions: 0.05 mmol **1**, 0.1 mmol **2** and catalyst **K** (5 mol-%) in benzene (0.7 mL)/MTBE (0.3 mL). Isolated yield after column chromatography. *E*/*Z* ratio determined by ^{1}H NMR of the crude mixture. Enantiomeric excess determined by chiral HPLC. [a] The result in parentheses corresponds to the 1 mmol scale reaction.

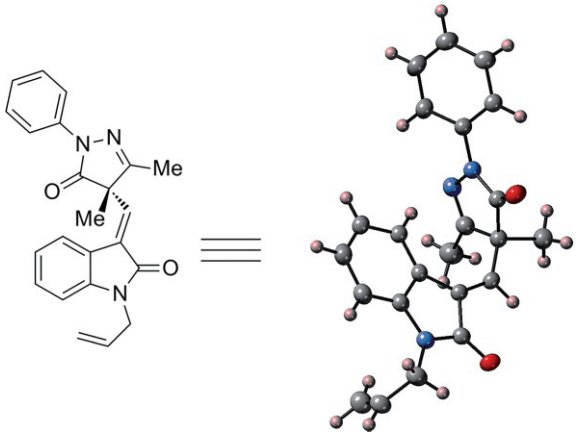
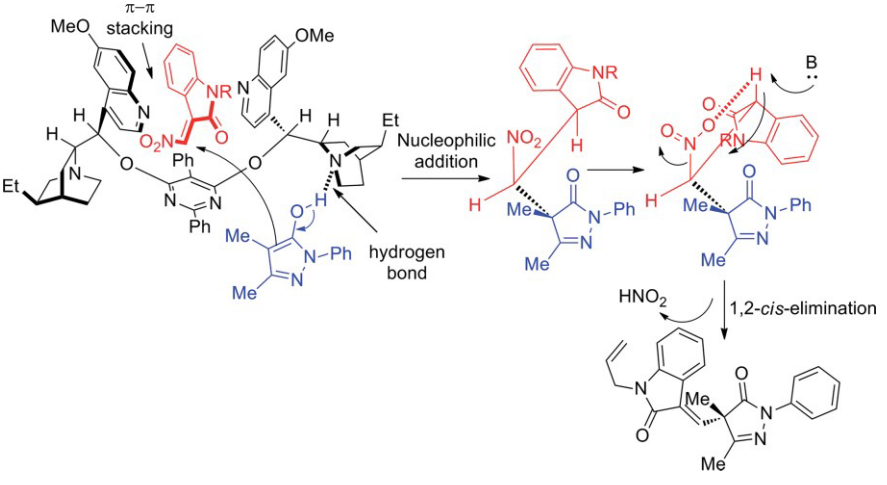


Figure 2. X-ray crystal structure of **3fa**.

On the basis of the absolute configuration of **3fa**, we propose a plausible mechanism for the stereoselective S$_N$V reaction as is shown in the Scheme 3. By the action of one quinuclidine moieties of (DHQ)$_2$Pyr, the pyrazol-3-one **2** is activated by hydrogen bonding, for the regioselective nucleophilic addition of the pyrazol-3-one to the *a*-position of nitroalkene **1**, that could be coordinated to the catalyst by *π*–*π* stacking interactions. After the nucleophilic addition of **2**, the intermediate switches to an eclipsed conformation, which is favored by an intramolecular hydrogen bond between the nitro group and the hydrogen of the C-3 of oxindole through a five-membered ring.[13,14] In this case, in the presence of a base [the quinuclidine moiety of the (DHQ)$_2$Pyr catalyst], the hydrogen bond prompts a fast 1,2-*cis*-elimination to afford the *E*-3-alkenyl-2-oxindole **3fa** as the major product.

Conclusions

We have developed a catalytic enantioselective addition of 4-substituted-pyrazolones to isatin-derived nitroalkenes catalyzed by (DHQ)$_2$Pyr, obtaining chiral pyrazolones bearing a quaternary stereocenter at 4 position with a 3-alkylidene-2-oxindole moiety with excellent yields (up to 97 %), excellent *E*/*Z* ratio (up



Scheme 3. Plausible reaction mechanism.

to > 20:1) and moderate enantioselectivities (up to 78 % ee). The reaction consists in a regioselective nucleophilic vinylic substitution (S_NV), where the nitro group acts as leaving group for delivering 3-alkylidene-2-oxindoles. The enantioselectivities are moderate, however taking into account that we obtain one of the several possible isomers, the present methodology represents an interesting synthetic way to obtain chiral 3-alkylidene-2-oxindoles. An advantage of our system is that the organocatalyst is commercially available and the reaction conditions are mild.

Acknowledgments

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Keywords: Asymmetric catalysis · Nitroalkenes · Pyrazolones · Organocatalysis · Nucleophilic substitution

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[16] Further optimization with catalyst **A** and **J** did not improve the results. See supporting information for further details.

[17] CCDC 1899761 (for **3fa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.