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# Direct and Enantioselective Vinylogous Michael Addition of α-Alkylidenepyrazolinones to Nitroolefins Catalyzed by Dual *Cinchona* Alkaloid Thioureas

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**Abstract:** While several protocols exist for the asymmetric functionalization of pyrazolinones at the α-position relying on nucleophilic addition or annulation procedures, use of α-alkylidene electron-rich analogues in asymmetric vinylogous coupling to carbon electrophiles is substantially an uncharted domain. We now report, for the first time, that alkylidenepyrazolinones carrying an enolizable carbon at the γ-position efficiently participate in direct and asymmetric, catalytic vinylogous Michael-type additions to nitroolefins providing the expected adducts in high yields, with complete γ-site selectivity and with extraordinary levels of enantio-, diastereo-, and geometrical selectivities. Both enantiomeric adducts were equally accessed by employing a *quasi*-enantiomeric quinine- or quinidine-based thiourea catalyst pair.

**Keywords:** asymmetric catalysis; *Cinchona* alkaloids; nitroolefins; organocatalysis; pyrazolinones; vinylogous Michael addition

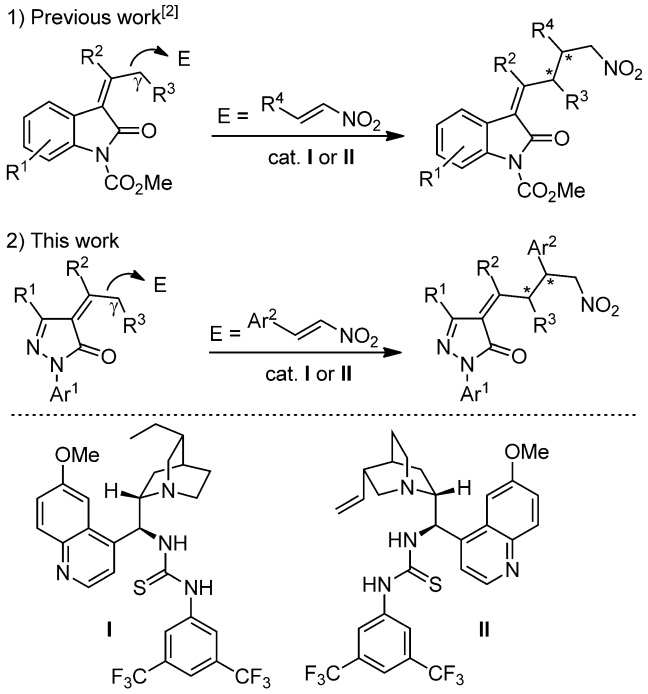
Five-membered nitrogen heterocycles and compounds embedding these motifs have long been recognized as privileged structural frameworks for the development of molecules with important biological and pharmaceutical properties. The pyrazole and pyrazolone nuclei subsets occupy a rewarding position in this scaffold realm, and many representatives are highly sought after in the context of drug discovery and agroscience.[1]

During our recent studies on the asymmetric vinylogous Michael-type reaction of α-alkylideneoxindoles,[2,3] we envisaged that the remote exocyclic γ-carbon of the substrates could be a suitable and exclusive nucleophilic site for the conjugate addition to β-nitroolefins by utilizing a dual *Cinchona*-based thiourea organocatalyst and its chiral surrounding for synergistic substrate activation and enantioinduction [Scheme 1, Eq. (1)].[4]

In this way variously shaped oxindole nitroadducts were assembled with extraordinary catalytic reactivity and selectivity. As part of our ongoing program towards the exploration of the vinylogous reactivity space of nitrogen-embedding heterocycles in catalytic, asymmetric carbon-carbon bond forming reactions, we report here, for the first time, that olefinic pyrazolinones also engage in catalytic, direct and asymmetric vinylogous Michael additions with a diverse range of nitroalkenes to furnish the respective adducts with admirable levels of regio-, enantio-, diastereo-, and geometrical selectivities [Scheme 1, Eq. (2)].[5,6]

We began by investigating the vinylogous Michael reaction of α-isopropylidenepyrazolinone **1a**, which was quickly obtainable from 3-methyl-1-phenyl-2-pyrazolin-5-one (edaravone, also coded as MCI-186), a free radical scavenger drug clinically used to reduce neuronal damage following cerebral ischemic stroke.[7] Evaluation of the dihydroquinine-derived thiourea catalyst **I** for the addition to *trans*-β-nitrostyrene (**2a**), using the conditions we previously reported for the asymmetric Michael reaction of 3-alkylideneoxin-



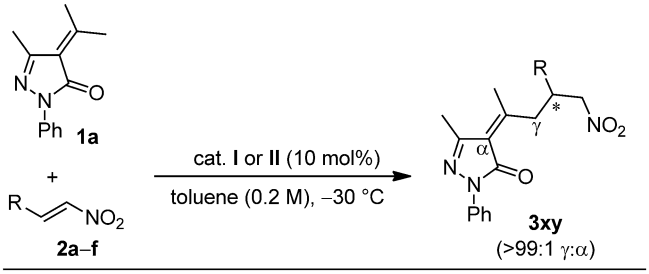

**Scheme 1.** Direct, organocatalyzed asymmetric vinylogous Michael reactions of nitrogen-embedding heterocycles. The vinylogous reactivity space involves the remote exocyclic γ-carbon of the pronucleophilic substrates.

doles,[2] yielded an encouraging initial result. When the reaction was conducted in toluene (0.2 M) at ambient temperature, nearly full conversion of the starting material was attained in less than 2 h, and adduct **3aa** was obtained in 80% yield, exhibiting a 6:1 *Z*/*E* isomeric ratio and a 97:3 *er*. To halt entirely the parasite background reaction which could erode the reaction selectivity, we lowered the temperature to −30 °C and, as was our hope, the reaction selectivity markedly improved, while maintaining high catalytic efficiency, and **3aa** was returned in a 93% isolated yield and as just one enantiomer (>99:1 *er*) and one geometrical isomer (>20:1 *Z*:*E* ratio) (Table 1, entry 1).

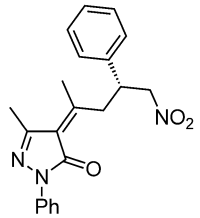
As expected, scrutinizing quinidine-based catalyst **II**, a *quasi*-enantiomer of **I**, under standardized conditions also underwent full substrate conversion, which returned the enantiomer of **3aa** (*ent*-**3aa**) in 89% yield, with 17:1 *Z*:*E* ratio, and 94:6 *er* (Table 1, entry 1′).

With these rewarding results established, we then wished to evaluate the scope and limitation of this process as regard to the nitroolefin acceptor. In addition to nitrostyrene **2a** leading to **3aa** and *ent*-**3aa**, a variety of differently substituted nitroolefins was first assayed in reactions with pyrazolinone **1a**. Excellent results were uniformly attained with aryl-substituted olefins and, whether they contain a neutral, an

**Table 1.** Substrate scope: variation of the nitroolefin acceptors with pyrazole donor **1a**, using catalysts **I** (normal entries) or **II** (primed entries).[a–d]

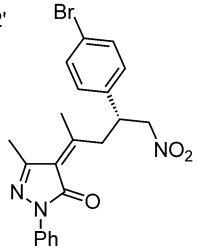



1/1'



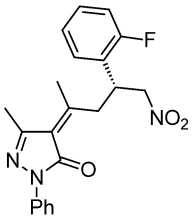
**3aa:** 93%, >20:1 (*Z*:*E*)
*er* = 99.7:0.3
*ent*-**3aa:** 89%, 17:1 (*Z*:*E*)
*er* = 94.1:5.9

2/2'



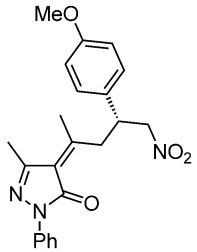
**3ab:** 79%, >20:1 (*Z*:*E*)
*er* = >99.9:0.1
*ent*-**3ab:** 78%, >20:1 (*Z*:*E*)
*er* = 99.5:0.5

3/3'



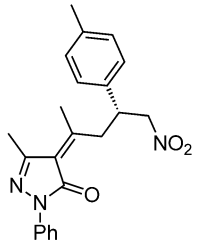
**3ac:** 73%, >20:1 (*Z*:*E*)
*er* = 99.7:0.3
*ent*-**3ac:** 74%, >20:1 (*Z*:*E*)
*er* = 98.8:1.2

4/4'



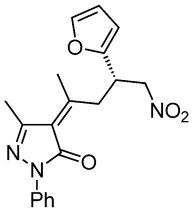
**3ad:** 74%, 17:1 (*Z*:*E*)
*er* = 99.9:0.1
*ent*-**3ad:** 71%, 16:1 (*Z*:*E*)
*er* = 93.2:6.8

5/5'



**3ae:** 81%, 14:1 (*Z*:*E*)
*er* = 99.3:0.7
*ent*-**3ae:** 76%, 16:1 (*Z*:*E*)
*er* = 84.3:15.7

6/6'



**3af:** 80%, >20:1 (*Z*:*E*)
*er* = 99.1:0.9
*ent*-**3af:** 78%, >20:1 (*Z*:*E*)
*er* = 97.1:2.9

[a] Reactions were performed with 0.47 mmol of **1** and 0.47 mmol of **2** in toluene (0.2 M) in the presence of catalysts **I** or **II** (10 mol%) at −30 °C for 24 h.
[b] Combined yield of isolated products.
[c] Diastereomeric ratios (*Z*:*E*) were determined by $^1$H NMR spectroscopy.
[d] Enantiomeric excesses of the major diastereoisomers were analyzed by HPLC using a chiral stationary phase column.

electron-withdrawing, or an electron-donating group, the desired adducts **3ab**–**3ae** were obtained in very good yields, almost complete geometrical selectivity in favor of the *Z*-configured isomers and with *er* values of >99:1 (entries 2–5). Moreover, we conducted the reactions between **1a** and heteroaromatic olefin **2f** leading to adduct **3af**, and equally rewarding results were obtained in terms of reactivity and selectivity (entry 6).

Reactions were duplicated with catalyst **II** to access the opposite enantiomeric series (Table 1, primed entries). In all cases, reactions performed well with respect to both the regio- and diastereocontrol, albeit they displayed slightly reduced enantioselectivities; and this reflects the diastereomeric nature of the two *Cinchona* alkaloid-based catalysts employed, not exactly an enantiomeric pair.[8]

The addition to β-alkyl-substituted nitroalkenes as well as the use of congested β,β-disubstituted congeners were also evaluated. We found that these substrates, which are known to be less prone to nucleophilic addition reactions,[9] were significantly less reactive than the (hetero)aryl-substituted nitroalkenes in our processes and, under the conditions shown in Table 1, no reaction was observed using β-cyclohexyl- and β-*n*-butyl-substituted nitroalkenes as well as α-methyl-β-nitrostyrene even after extended reaction times or raising the reaction temperature and catalyst loading. Importantly, we carried out the reactions towards **3aa** on a 1.0 mmol scale, and found that the reactivity and geometry control, as well as the site selectivity and enantioselectivity, remained excellent.

The applicability of the reaction with different ylidenepyrazolinones was next explored under the above established conditions, using either unsubstituted styrene **2a** or the brominated counterpart **2b**. Substrates with substituents on the pyrazole *N*-phenyl group invariably gave good yields ranging from 80% to 91% (Table 2, entries 1–6), irrespective of their electronic nature. No significant influence was observed on the enantio- and geometrical selectivities, whose levels remained rewarding in all cases. Changing the methyl substituent at the pyrazole C-3 position to *n*-propyl or phenyl groups was also tolerated, allowing access to *Z*-configured nitroadducts **3ea** and **3fa** in 71–75% yields and with exceptional margins of enantio- and geometrical selectivities (entries 7 and 8). Use of prochiral symmetrical diethyl-substituted ylidene substrate **1g** and unsymmetrical methyl-ethyl substituted analogue **1h**, where two adjacent stereocenters were installed simultaneously, was also suited to this reaction, which afforded the corresponding adducts **3ga** and **3ha** in excellent yields and selectivities (entries 9 and 10). The result with precursor **1h** is particularly impressive: of the two different enolizable γ,γ′-carbon sites ($CH_3$ and $C_2H_5$) only the ethylene group participated in the addition, giving rise to the *Z*-configured adduct **3ha** as the sole enantiomer and diastereoisomer (>20:1 *anti/syn*, >99:1 *er*).[10] As for the experiments grouped in Table 1, reactions were run in parallel with quasi-enantiomeric catalyst **II** to enter the opposite enantiomeric adducts, and the results are displayed in the primed entries of Table 2. Invariably, reactions were high-performing, showing an excellent control of the product geometry and diastereoselectivity, albeit suffering, in some instances, from a minute drop in enantioselectivity.

The relative configuration of **3ha**, carrying two consecutive stereogenic centers, was unambiguously determined as (*Z*)-3′,4′-*anti via* single crystal X-ray diffraction analysis (Figure 1).[11] The absolute configuration of products **3** was tentatively assumed (*R*-configured from **I**, *S*-configured from **II**)[12] by analogy to the previous work on nucleophilic vinylogous addition to nitroolefins catalyzed by **I** and **II**.[2] However, an indirect, though reliable assignment of the **3aa** structure was carried out *via* $OsO_4$/$PhI(OAc)_2$-assisted oxidative fission of the exocyclic double bond to give a known nitroketone product, as detailed in the Supporting Information. The *Z*/*E* geometry of products **3** was also corroborated by proton nuclear Overhauser effect spectroscopy measurements.

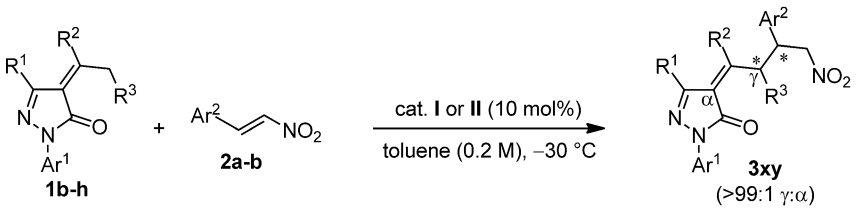
Based on the observed stereochemistry of the Michael adducts and capitalizing on previous studies on closely related organocatalytic transformations,[2,4] a plausible mechanistic itinerary for the present conjugate addition was proposed (Figure 2). We postulated that the pendent tertiary amine of the bifunctional catalyst **I** (or **II**) first deprotonates the alkylidenepyrazolones at the γ-position, and that the protonated catalyst then brings the dienolate nucleophile and the alkene electrophile together to give a tight H-bonded ternary complex with the right alignment of the reactants to ensure a precise control during the key carbon-carbon bond formation.

Specifically, linking the nitroolefin to the two NH groups of the thiourea moiety and the pyrazole dienolate to the quinuclidinium portion of the catalyst produces a stereo-determining transition state which results in the formation of the γ-alkylated products predominantly, *via* preferential acceptor *Re*-face addition trajectory (catalyst **I**), consistent with the experimental observations. We rationalize that the *s-cis* conformational preference of the transient dienolate controls the double bond geometry of the adducts, while the prevalence for γ- over α-alkylation might likely be the result of stereoelectronic influences.

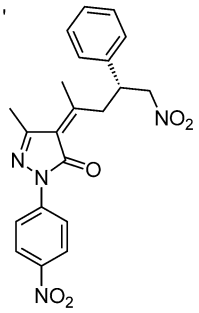
Moreover, our model to explain the reaction diastereoselectivity using prochiral ylidene substrates (*anti vs. syn*) is consistent with the observation that, in the stereo-determining step, the active dienolate species assumes a favorable *Z*-geometry, which translates completely into the *anti* configuration in the addition products.[13]

**Table 2.** Substrate scope: variation of pyrazole donors with olefins **2a** or **2b** as acceptors, using catalysts **I** (normal entries) or **II** (primed entries).[a]

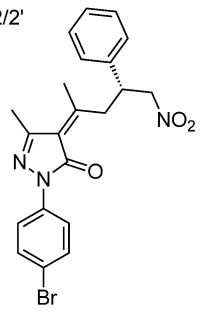



1/1'



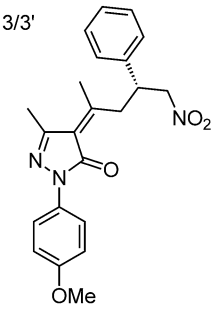
**3ba:** 91%, >20:1 (*Z*:*E*)
*er* = 98.8:1.2
*ent*-**3ba:** 78%, >20:1(*Z*:*E*)
*er* = 96.4:3.6

2/2'



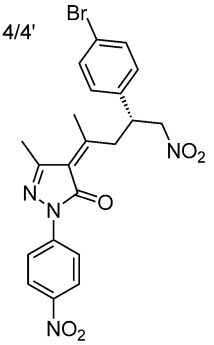
**3ca:** 90%, 12:1 (*Z*:*E*)
*er* = 99.9:0.1
*ent*-**3ca:** 91%, 14:1 (*Z*:*E*)
*er* = 99.1:0.9

3/3'



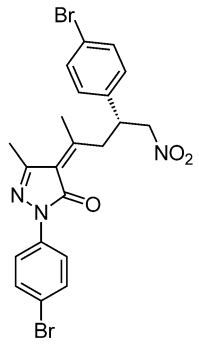
**3da:** 80%, >20:1 (*Z*:*E*)
*er* = >99.9:0.1
*ent*-**3da:** 75%, >20:1 (*Z*:*E*)
*er* = 85.1:14.9

4/4'



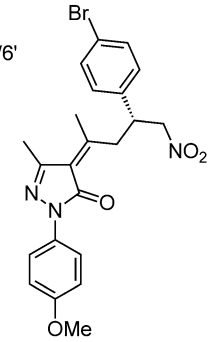
**3bb:** 89%, >20:1 (*Z*:*E*)
*er* = 99.0:1.0
*ent*-**3bb:** 75%, >20:1 (*Z*:*E*)
*er* = 95.0:5.0

5/5'



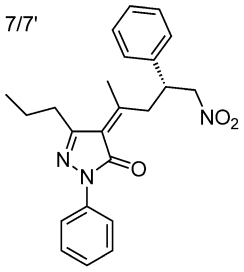
**3cb:** 87%, >20:1 (*Z*:*E*)
*er* = 99.9:0.1
*ent*-**3cb:** 80%, >20:1 (*Z*:*E*)
*er* = 94.6:5.4

6/6'



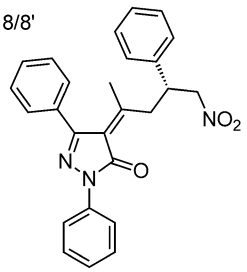
**3db:** 90%, 14:1 (*Z*:*E*)
*er* = 96.9:3.1
*ent*-**3db:** 82%, 15:1 (*Z*:*E*)
*er* = 96.1:3.9

7/7'



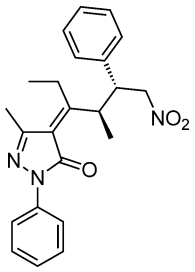
**3ea:** 75%, 14:1 (*Z*:*E*)
*er* = 98.4:1.6
*ent*-**3ea:** 71%, 11:1 (*Z*:*E*)
*er* = 93.6:6.4

8/8'



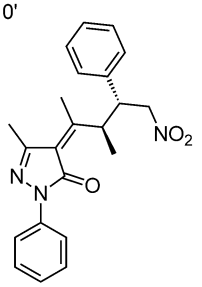
**3fa:** 71%, >20:1 (*Z*:*E*)
*er* = 98.8:1.2
*ent*-**3fa:** 69%, 16:1 (*Z*:*E*)
*er* = 97.5:2.5

9/9'



**3ga:** 85%, >20:1 (*Z*:*E*)
>20:1 (*anti*:*syn*)
*er* = 98.4:1.6
*ent*-**3ga:** 81%, >20:1 (*Z*:*E*)
>20:1 (*anti*:*syn*)
*er* = 96.6:3.4

10/10'



**3ha:** 91%, >20:1 (*Z*:*E*)
>20:1 (*anti*:*syn*)
*er* = 98.6:1.4
*ent*-**3ha:** 77%, >20:1 (*Z*:*E*)
>20:1 (*anti*:*syn*)
*er* = 96.0:4.0

[a] For conditions and measurements, see footnotes in Table 1.

A salient feature of the present asymmetric vinylogous Michael addition is that it provides products in which the exocyclic unsaturation of the initial pyrazolinone substrate is preserved. This olefinic function could in turn be used to further manipulate the system, thus increasing the molecular complexity of the pyrazole products. As an example (Scheme 2), enantiomerically pure pyrazolinone **3ha** was stereoselectively elaborated into a rare oxopyrazoline spirooxirane **4**, as a single isomer, by subjecting the olefin to nucleophilic $H_2O_2$ epoxidation,[14] a manoeuver that completes the installation of four consecutive stereogenic carbon centers, two of which are quaternary. The stereochemistry of oxirane **4** was determined to be *cis via* 2D-NOESY experiments, as detailed in the Supporting Information.

In summary, we have developed the first highly enantioselective, diastereoselective, and geometry-selective direct vinylogous Michael addition between α-alkylidenepyrazolinones and nitroalkenes catalyzed by readily available *Cinchona* alkaloid-based bifunctional thioureas. Under our optimized reaction conditions, site-specific functionalization at the remote γ-carbon of the pyrazole scaffold was realized to provide a range of structurally diverse *Z*-configured Michael adducts with extraordinary levels of selectivity for both the enantiomers. Further investigations, which involve the use of diverse nucleophilic and pro-

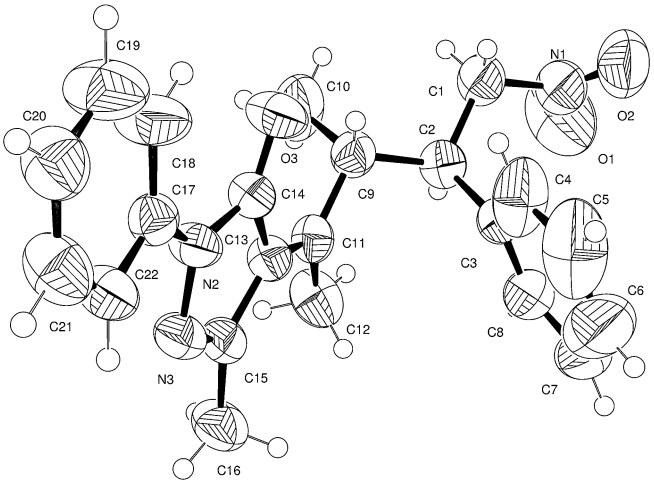



**Figure 1.** ORTEP drawing of compound **3ha** as determined by single crystal X-ray analysis.

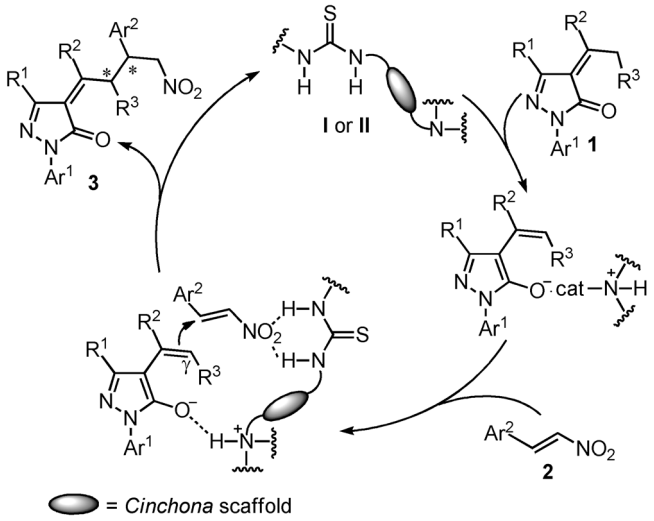
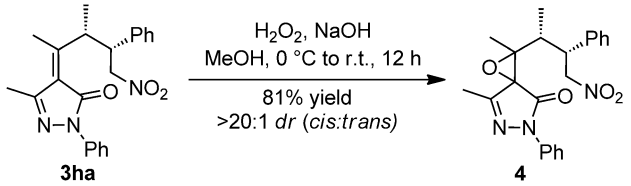



**Figure 2.** Proposed organocatalytic cycle for the vinylogous 1,4-addition of olefinic pyrazolinones to nitroolefins. The *Z*-geometry of the prochiral dienolate translates into the *anti* configuration of the product. The *s-cis* conformation of the pyrazole dienolate results in a *Z*-configured double bond in the adduct.




**Scheme 2.** Nucleophilic epoxidation of pyrazolinone **3ha** to tetrasubstituted *cis*-spirooxirane **4**.

nucleophilic heterocyclic candidates in other asymmetric vinylogous and multivinylogous functionalization reactions, are ongoing and will be reported in due course.

# Experimental Section

### Representative Procedure for the Synthesis of 3aa

To a solution of pyrazolinone **1a** (100 mg, 0.47 mmol, 1.0 equiv.) and nitrostyrene **2a** (70 mg, 0.47 mmol, 1.0 equiv.) in toluene (2.35 mL), cooled at −30 °C, was added thioureacatalyst **I** (28 mg, 0.047 mmol, 0.1 equiv.). The reaction was kept under vigorous stirring at −30 °C for 24 h. After warming to room temperature, the reaction solution was passed through a celite pad, concentrated under vacuum, and the crude product was purified by silica gel flash chromatography (80:20 hexane/EtOAc) to yield pure (*R,Z*)-**3aa** as an orange solid; yield: 159 mg (93%). The *dr* (*Z:E*) of the product was determined to be >20:1 by $^1$H NMR analysis of the crude reaction mixture; mp 118–122 °C; $[\alpha]_D^{20}$: −33.6 (*c* 1.4, chloroform); $R_f$ = 0.38 (80:20 hexane/EtOAc). Chiral HPLC (Chiracel OD-H, hexane/ethanol 90:10, 1.0 mL min$^{-1}$, 254 nm): $R_t$ 17.79 min (major), 21.86 min (minor) (99.7:0.3 *er*). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.90 (m, 2H, arom), 7.13–7.45 (m, 8H, arom), 4.76 (dd, 1H, *J* = 12.9, 8.7 Hz, H-5′a), 4.71 (dd, 1H, *J* = 12.9, 6.5 Hz, H-5′b), 4.00 (dd, 1H, *J* = 12.0, 7.4 Hz, H-3′a), 3.86 (dddd, 1H, *J* = 8.7, 8.1, 7.4, 6.5 Hz, H-4′), 3.06 (dd, 1H, *J* = 12.0, 8.1 Hz, H-3′b), 2.36 (s, 3H, C3-Me), 2.18 (s, 3H, C1′-Me); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.8 (Cq), 163.0 (Cq), 148.0 (Cq), 138.7 (Cq), 137.9 (Cq), 129.0 (2C, CH), 128.8 (2C, CH), 128.7 (Cq), 128.1 (CH), 127.5 (2C, CH), 125.1 (CH), 119.2 (2C, CH), 79.6 ($CH_2$), 43.2 (CH), 38.4 ($CH_2$), 23.0 (Me), 19.0 (Me); HR-MS (ESI): *m/z* = 364.1669, calcd. for $C_{21}H_{22}N_3O_3$ $[M+H]^+$: 364.1661.

### Supporting Information

Experimental procedures, characterization, spectroscopic data, X-ray crystal structure of **3ha**, HPLC profiles, and copies of $^1$H and $^{13}$C NMR spectra are available in the Supporting Information.

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[8] The precise reason for the observed marginal decline of the asymmetric induction with catalyst **II** as compared to **I** has not been determined, but maybe because the chirality resident in the quinuclidine portion (C-4 and C-8), equal for both, also plays a role in the chirality transmission from the catalyst to the product.

[9] The inertia displayed by β-alkyl-substituted nitroalkenes compared to their β-(hetero)aryl counterparts in related conjugated additions has been observed previously. See, for example: a) Y.-n. Xuan, S.-z. Nie, L.-t. Dong, J.-m. Zhang, M. Yan, *Org. Lett.* **2009**, *11*, 1583–1586; b) A. Noole, I. Järving, F. Werner, M. Lopp, A. Malkov, T. Kanger, *Org. Lett.* **2012**, *14*, 4922–4925; c) D. Enders, R. Hahn, I. Atodiresei, *Adv. Synth. Catal.* **2013**, *355*, 1126–1136.

[10] Actually, **1h** was a 80:20 mixture of *Z* and *E* isomers, however the result proved independent of the starting olefin geometry. Equal results were obtained using a 50:50 *Z/E* mixture.

[11] Lacking heavy atoms, the assignment of the absolute configuration of **3ha** could not be exactly determined [Flack parameter for the (*R,R*)-isomer was 0.102(602)]. CCDC 986579 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

  

[or from the Cambridge Crystallographic Data Centre 12, Union Road, Cambridge CB2 1EZ, U.K.; fax: (+ 44)-1223-336-033; or deposit@ccdc.cam.ac.uk].

[12] Assuming that the olefin facial selectivity imparted by the catalyst was the same for all the reactions (*Re*-face from **I**; *Si*-face from **II**), the absolute configuration of the products **3** is 4*R* while that of products *ent*-**3** is 4*S*. However, due to IUPAC substituent priority rules, adduct **3af** is *S*-configured; *ent*-**3af** is *R*-configured.

[13] An alternative dual activation channel cannot in principle be excluded. According to the proposals of Pápai and Zhong, the nucleophile could be activated by the thiourea group of the catalyst, while the protonated quinuclidine nitrogen engenders a bifurcate H-bonding with the nitroolefin. See: a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151–13160; b) B. Tan, Y. Lu, X. Zeng, P. J. Chua, G. Zhong, *Org. Lett.* **2010**, *12*, 2682–2685.

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**8** Direct and Enantioselective Vinylogous Michael Addition of α-Alkylidenepyrazolinones to Nitroolefins Catalyzed by Dual *Cinchona* Alkaloid Thioureas

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