OL Organic Letters

pubs.acs.org/OrgLett

Letter

Catalytic Diastereo- and Enantioselective Vinylogous Mannich Reaction of Alkylidenepyrazolones to Isatin-Derived Ketimines

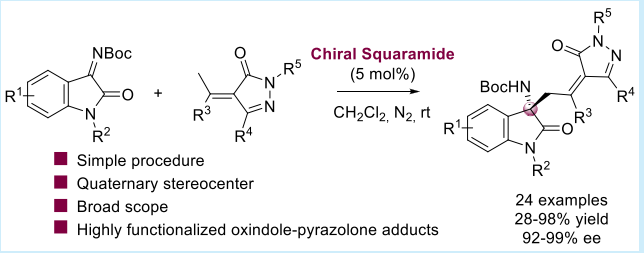
Laura Carceller-Ferrer, Carlos Vila, Gonzalo Blay,* M. Carmen Muñoz, and José R. Pedro*

Cite This: *Org. Lett.* 2021, 23, 7391−7395

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A valuable organocatalytic vinylogous Mannich reaction between alkylidenepyrazolones and isatin-derived ketimines has been successfully established. Squaramide organocatalyst, prepared from quinine, catalyzed the diastereo- and enantioselective vinylogous Mannich addition, affording a range of aminooxindole-pyrazolone adducts (24 examples) with excellent outcomes: up to 98% yield with complete diastereoselectivity and excellent enantioselectivity (up to 99% ee). Additionally, different synthetic transformations were performed with the chiral pyrazolone-oxindole adducts.

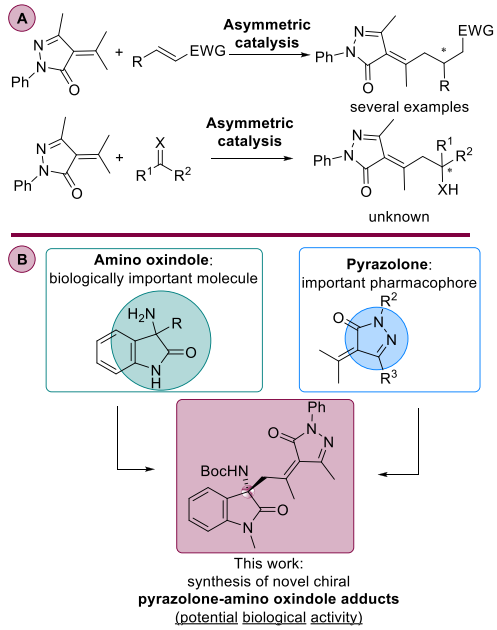


The direct catalytic asymmetric vinylogous reaction represents a powerful tool in synthetic organic chemistry to introduce stereocenters at the γ-position or even more remote positions of the functional groups in organic compounds in an atom-economical and efficient way.[1] In this research area, the asymmetric vinylogous Mannich reaction is a powerful, direct, and straightforward C−C bond-forming reaction leading to the synthesis of optically active δ-amino-α,β-unsaturated carbonyl derivatives.[1d] This class of compounds is a significant building block for the synthesis of biologically active compounds and drugs.

On the contrary, pyrazolone derivatives represent one of the most important five-membered heterocycles containing nitrogen atoms, which are present in several bioactive natural products and pharmaceuticals.[2] Therefore, the enantioselective synthesis of chiral pyrazolones has received the attention of the synthetic organic chemists in the last several years.[3] In this context, the asymmetric vinylogous nucleophilic γ-addition of α,β-unsaturated pyrazolone bearing γ-hydrogen atoms to electrophiles has been explored for the construction of chiral pyrazolones. However, these examples are restricted to the use of α,β-unsaturated compounds[4] or Morita−Baylis−Hillman carbonates[5] as electrophiles. As far as we know, the corresponding asymmetric nucleophilic 1,2-addition of alkylidenepyrazolones to carbonyl compounds or imines has not yet been described in the literature (Scheme 1A).

During our recent studies on the enantioselective Mannich addition of pyrazolones to imines,[6] we envisioned that the corresponding asymmetric vinylogous Mannich reaction could be feasible. Using α-isopropylidenepyrazolone as a nucleophile, remote γ-exocyclic functionalization of the diazaheterocycle could be possible using isatin-derived ketimines as electrophiles and bifunctional organocatalysis. The nucleophilic addition to isatin-derived ketimines constitutes a straightfor-

Scheme 1. Asymmetric Vinylogous Alkylation of Alkylidenepyrazolones



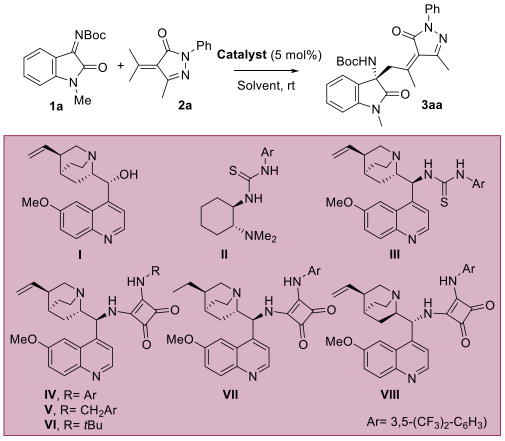
Received: August 2, 2021
Published: September 23, 2021

https://doi.org/10.1021/acs.orglett.1c02571
Org. Lett. 2021, 23, 7391−7395

ward methodology to synthesize enantioenriched amino oxindole compounds.[7] Numerous natural products and pharmacologically active compounds contain in their structures the amino-oxindole scaffold, showing the importance of this structural motif in synthetic organic chemistry.[8] In light of the pharmacological and biological activities of pyrazolones and amino oxindoles, the combination of both structural motifs into one molecule could result in novel and interesting chiral alkylidenepyrazolones bearing a quaternary aminooxindole stereocenter that may be useful for drug discovery (Scheme 1B).[9]

Initially, we selected the enantioselective vinylogous Mannich reaction of α-isopropylidenepyrazolone **2a**, which was easily prepared from the commercially available edaravone and acetone, and isatin-derived *N*-Boc ketimine **1a** in CH_2Cl_2 at room temperature. With these conditions, several bifunctional organocatalysts were tested, and the results are summarized in Table 1. We selected bifunctional organocatalysts[10] with a tertiary amine responsible for the activation of the nucleophile (deprotonation of the γ-hydrogens of the α,β-unsaturated pyrazolone) and a hydrogen-bonding donor moiety with the purpose of activating the electrophile (the isatin-derived *N*-Boc ketimine). When quinine (**I**) was used as catalyst, the yield of the Mannich product **3aa** was very low (6%), but the enantioselectivity was moderate (50% ee). We observed large amounts of *N*-methylisatine from the hydrolysis of ketimine **1a**. Takemoto's thiourea **II** and quinine-derived thiourea **III** exhibited high stereocontrol (90% ee); however, the yield of product **3aa** was still low (~20%). Delightfully, quinine-derived squaramide **IV** gave excellent enantiomeric excess (98%), and the yield increased to 42% after 3 days of reaction (entry 4). When benzylic (**V**)- and *tert*-butyl (**VI**)-substituted squaramides were used as catalysts, product **3aa** was obtained in similar yield but with somewhat lower enantioselectivity. The squaramide **VII**, prepared from dihydroquinine, displayed similar reactivity and stereoselectivity, and product **3aa** was obtained in 41% yield with 97% *ee* after 3 days. Squaramide **VIII**, prepared from quinidine, gave a similar yield (39%) and enantiomeric excess (96% ee) as quinine-based **IV**, but the opposite enantiomer was obtained. We chose **IV** to continue the optimization process of the reaction conditions. Different solvents were tested, achieving high enantioselectivities but lower yields than CH_2Cl_2 (entries 9−13). To improve the yield of the reaction, we studied the variation of the equivalents of the electrophile (entry 14) or nucleophile (entry 15); however, the yields were lower. We observed in all cases the formation of *N*-methyl isatin, the corresponding hydrolysis product of **1a**. To avoid the hydrolysis of the ketimine and increase the yield, we performed the reaction under an anhydrous nitrogen atmosphere (entry 16). In this case, the yield of the Mannich product **3aa** increased to 57%, maintaining the enantioselectivity (98%). Finally, we increased the reaction scale to 0.2 mmol and obtained similar results (entry 17).

Table 1. Optimization of the Reaction Conditions[a]



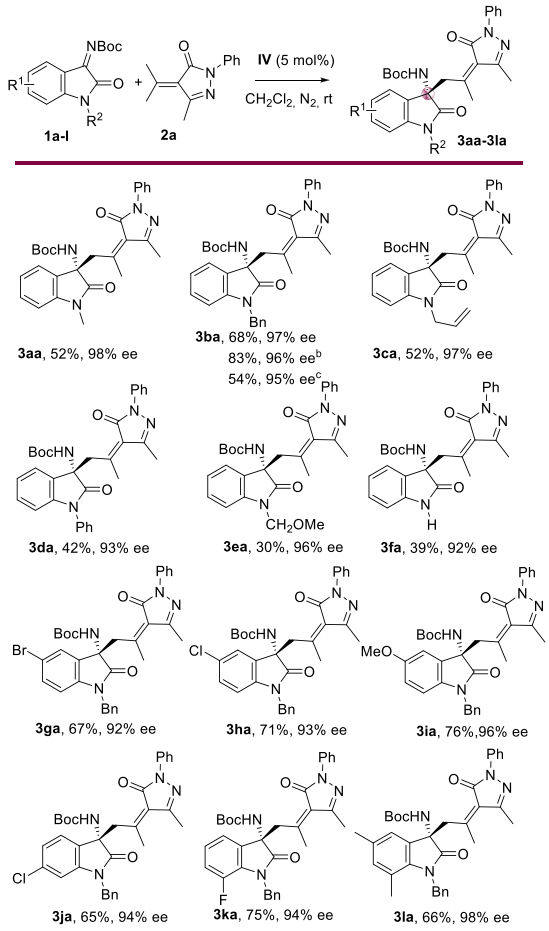
entry	catalyst	solvent	*t* (days)	yield (%)[b]	ee (%)[c]
1	**I** (5%)	CH_2Cl_2	4	6	50
2	**II** (5%)	CH_2Cl_2	4	16	91
3	**III** (5%)	CH_2Cl_2	3	19	89
4	**IV** (5%)	CH_2Cl_2	3	42	98
5	**V** (5%)	CH_2Cl_2	3	41	92
6	**VI** (5%)	CH_2Cl_2	3	44	94
7	**VII** (5%)	CH_2Cl_2	3	41	97
8	**VIII** (5%)	CH_2Cl_2	3	39	96[d]
9	**IV** (5%)	$ClCH_2CH_2Cl$	3	40	96
10	**IV** (5%)	$CHCl_3$	3	28	97
11	**IV** (5%)	EtOAc	3	33	91
12	**IV** (5%)	Et_2O	3	55	92
13	**IV** (5%)	toluene	3	42	95
14[e]	**IV** (5%)	CH_2Cl_2	3	38	97
15[f]	**IV** (5%)	CH_2Cl_2	3	42	97
16[g]	**IV** (5%)	CH_2Cl_2	3	57	98
17[g,h]	**IV** (5%)	CH_2Cl_2	3	52	98

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), and 5 mol % of organocatalyst in 1 mL of solvent at rt under an air atmosphere. [b]Isolated yield of **3aa** after column chromatography. [c]Determined by chiral HPLC. [d]Opposite enantiomer was obtained. [e]0.12 mmol of **1a** was used. [f]0.12 mmol of **2a** was used. [g]Reaction was performed under a N_2 atmosphere. [h]Reaction was performed on a 0.2 mmol scale.

With the optimized reaction conditions in hand (entry 16, Table 1), we evaluated the scope of the vinylogous Mannich reaction with an assortment of isatin-derived ketimines **1** with several substituents in different positions (Scheme 2). Initially, substitution with different groups such as methyl, benzyl, or allyl at the N-1 of the oxindole was evaluated (**3aa**−**3fa**), providing the corresponding products in good yields (52−68%) with high enantioselectivities (97−98% ee). We also tested isatin-derived ketimines with Ph, $-CH_2OMe$, and H substituents at the N-1 and obtained excellent enantioselectivities (92−96% ee) but lower yields (30−42%). Because the best yield was obtained with *N*-benzyl isatin-derived ketimines, we evaluated the effect of the substitution pattern of several *N*-benzylisatines. Electron-withdrawing (Br or Cl) or electron-donating (MeO) groups were tolerated at the five-position of the isatin-derived ketimine, affording the corresponding products **3ha** and **3ia** in good yields with excellent enantioselectivities in all cases. However, with the ketimine prepared from 5-bromoisatin, the yield was low (28%). Furthermore, isatin-derived ketimines with substituents at the six- or seven-positions reacted efficiently, providing the Mannich products **3ja** and **3ka** in good yields (67−75%) with excellent stereoselectivities. Also, the disubstituted ketimine **1l** could be used, affording the corresponding product **3la** with excellent enantioselectivity (98% ee) in 66% yield. The reaction could be accomplished on a 1 mmol scale, improving the yield of product **3ba** (83%) and maintaining the enantioselectivity of the reaction (96% ee). We also tested the reaction on a 1 mmol scale lowering the

https://doi.org/10.1021/acs.orglett.1c02571
Org. Lett. 2021, 23, 7391−7395

Scheme 2. Scope of the Catalytic Enantioselective Vinylogous Addition of Alkylidenepyrazolone 2a to Isatin-Derived Ketimines 1[a]



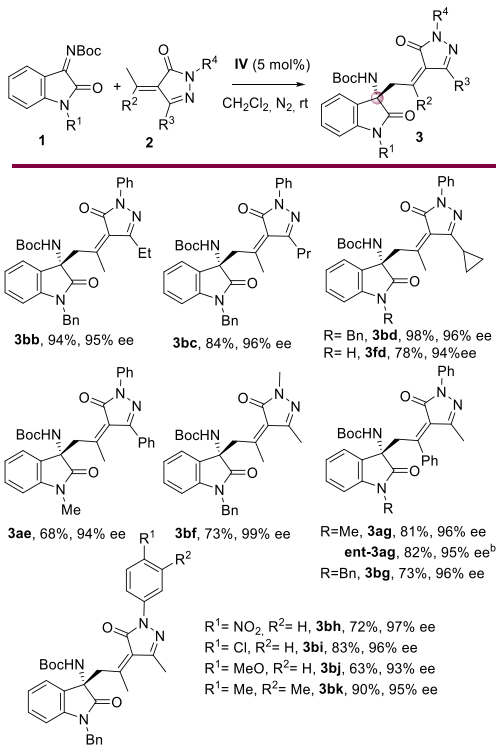
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), and **IV** (5 mol %) in 1 mL of CH_2Cl_2 at rt under a N_2 atmosphere. Isolated yield of **3** after column chromatography. Determined by chiral HPLC. [b]1 mmol scale reaction using 5 mol % of **IV**. [c]1 mmol scale reaction using 2 mol % of **IV**.

catalyst amount to 2 mol % of **IV**. In this case, we observed a similar enantioselectivity (95% ee) but a lower yield (54%).

Next, we turned our attention to further explore the substrate scope with respect to the alkylidenepyrazolones **2** (Scheme 3). Alkyl groups (Et, Pr, and cyclopropyl) other than Me were well tolerated at the five-position of the pyrazolones (**3bb**−**3bd**), providing excellent yields (84−98%) and enantioselectivities (95−96% ee). 2,5-Diphenyl and 2,5-dimethyl alkylidenepyrazolone were also examined under the optimized reaction conditions, providing products **3ae** in 68% yield with 94% ee and **3bf** in 73% yield with 99% ee. Moreover, when alkylidenepyrazolone derived from acetophenone was tested with ketimines **1a** and **1b**, the corresponding Mannich products **3ag** and **3bg** were obtained with excellent results. Finally, the reaction proceeded efficiently with pyrazolones with different substituents (NO_2, Cl, Me, and MeO) on the *N*-aryl group, providing the corresponding products in high yields (63−90%) with high enantiomeric excesses (93−97% ee).

The double-bond configuration and absolute configuration of the stereogenic center present in compound **3ea** were ascertained to be (S, Z) by X-ray crystallographic analysis

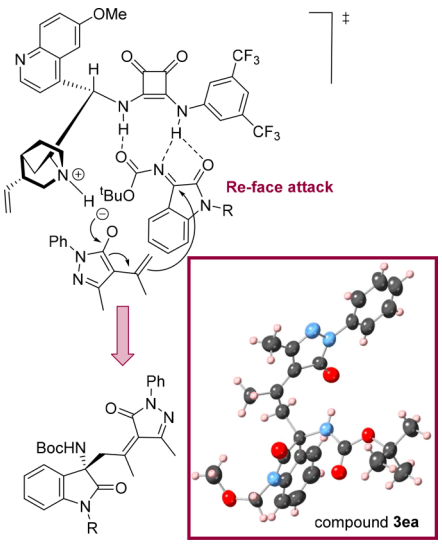
Scheme 3. Scope of the Catalytic Enantioselective Vinylogous Addition of Alkylidenepyrazolone 2 to Isatin-Derived Ketimines 1[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.2 mmol), and **IV** (5 mol %) in 1 mL of CH_2Cl_2 at rt under a N_2 atmosphere. Isolated yield of **3** after column chromatography. Determined by chiral HPLC. [b]**VIII** was used.

(Scheme 4); the configuration of the remaining Mannich products **3** was assigned on the assumption of a uniform mechanistic reaction pathway. A plausible transition-state model is illustrated in Scheme 4, where the squaramide catalyst **IV** is responsible for the preorientation and the

Scheme 4. Proposed Reaction Mechanism for the Asymmetric Vinylogous Mannich Reaction and X-ray Crystal Structure of 3ea

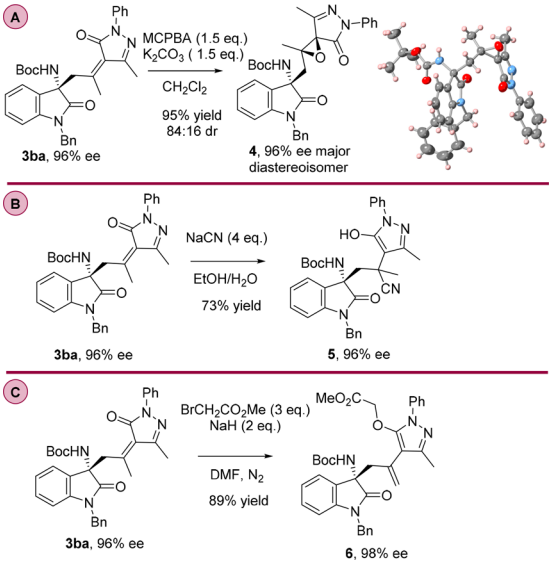


https://doi.org/10.1021/acs.orglett.1c02571
Org. Lett. 2021, 23, 7391−7395

activation of the substrates of the reaction. Whereas the methyl group of alkylidenepyrazolones is first deprotonated by the quinuclidine moiety of the organocatalyst to form the corresponding diene enolate, the isatin-derived *N*-Boc-ketimine moiety is activated upon the formation of hydrogen bonds between the *N*-Boc group and the squaramide moiety of the organocatalyst. The pyrazolone enolate will be directed to the *Re*-face of the ketimine, thus accounting for the observed enantioselectivity.

To demonstrate the versatility and usefulness of our organocatalytic vinylogous methodology, we performed several chemical modifications of the Mannich products (Scheme 5).

Scheme 5. Synthetic Transformations



A relevant structural feature of the obtained vinylogous Mannich adducts is that they preserve the exocyclic unsaturation of the initial pyrazolone substrate. This olefinic group could be used to further functionalize the compound, thus increasing the molecular complexity of the pyrazolone products. For example, compound **3ba** was stereoselectively epoxidated with *meta*-chloroperoxybenzoic acid (mCPBA), affording the spirooxirane **4** (Scheme 5A) with three quaternary stereocenters in 90% yield with good diastereoselectivity (84:16 dr) and maintaining the enantiomeric excess.[11] We could obtain crystals of the major diastereoisomer **4**, which allowed us to determine the configuration of the epoxide. Moreover, compound **3ba** could be subjected to a conjugate addition of NaCN,[12] providing the corresponding product **5** as a single diastereoisomer in good yield (73%) and maintaining the enantiomeric excess (Scheme 5B). Finally, the reaction of compound **3ba** with methyl bromoacetate in the presence of NaH[13] afforded the highly functionalized chiral pyrazole **6** in 89% yield and preserved the optical purity of the starting material (Scheme 5C).

In summary, we have established an organocatalytic diastereo- and enantioselective vinylogous Mannich reaction of alkylidenepyrazolones with isatin-derived ketimines using a quinine-derived squaramide organocatalyst, obtaining the corresponding chiral Mannich adducts in moderate to high yields (up to 98%) with complete diastereoselectivities toward the Z double bond and excellent enantioselectivities (up to 99% ee) under mild reaction conditions. The reaction showed a wide substrate scope for different *N*-Boc-ketimines and alkylidenepyrazolones. The new compounds feature pyrazolone and amino-oxindole moieties, which are privileged structures in medicinal chemistry. Moreover, several synthetic transformations of the chiral Mannich product **3ba** have been performed, showing the potential applicability of the present methodology. Studies on extending the scope of the reaction are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02571.

Complete experimental procedures and characterization of new products and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

Accession Codes

CCDC 2092891−2092892 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

Gonzalo Blay − *Departament de Química Orgànica, Facultat de Química, Universitat de València, 46100 València, Spain;* orcid.org/0000-0002-7379-6789; Email: gonzalo.blay@uv.es

José R. Pedro − *Departament de Química Orgànica, Facultat de Química, Universitat de València, 46100 València, Spain;* orcid.org/0000-0002-6137-866X; Email: jose.r.pedro@uv.es

Authors

Laura Carceller-Ferrer − *Departament de Química Orgànica, Facultat de Química, Universitat de València, 46100 València, Spain*

Carlos Vila − *Departament de Química Orgànica, Facultat de Química, Universitat de València, 46100 València, Spain;* orcid.org/0000-0001-9306-1109

M. Carmen Muñoz − *Departament de Física Aplicada, Universitat Politècnica de València, 46022 València, Spain;* orcid.org/0000-0003-2630-3897

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c02571

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Agencia Estatal de Investigación (AEI, Spanish Government) and Fondo Europeo de Desarrollo Regional (FEDER, European Union) (PID2020-116944GB) and from Conselleria d'Innovació, Universitat, Ciència i Societat Digital (AICO/2020/68) is acknowledged. L.C.-F. thanks the Universitat de València for a predoctoral grant. C.V. thanks the Spanish Government for a RyC contract (RYC-2016-20187). Access to the NMR, MS, and X-ray facilities

from the Servei Central de Suport a la Investigació Experimental (SCSIE)-UV is also acknowledged.

REFERENCES

(1) For the principle of vinylogy, see: (a) Fuson, R. C. The Principle of Vinylogy. *Chem. Rev.* **1935**, *16*, 1. For selected reviews of asymmetric vinylogous reactions, see: (b) Li, H.; Yin, L. Recent progress on direct catalytic asymmetric vinylogous reactions. *Tetrahedron Lett.* **2018**, *59*, 4121. (c) Yin, Y.; Jiang, Z. Organocatalytic asymmetric vinylogous Michael reactions. *ChemCatChem* **2017**, *9*, 4306. (d) Sánchez-Roselló, M.; Del Pozo, C.; Fustero, S. A decade of advance in the asymmetric vinylogous Mannich reaction. *Synthesis* **2016**, *48*, 2553. (e) Schneider, C.; Abels, F. Catalytic, enantioselective vinylogous Michael reactions. *Org. Biomol. Chem.* **2014**, *12*, 3531. (f) Bisai, V. Organocatalytic asymmetric vinylogous aldol reactions. *Synthesis* **2012**, *44*, 1453. (g) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. The vinylogous aldol and related addition reactions: ten years of progress. *Chem. Rev.* **2011**, *111*, 3076. (h) Pansare, S. V.; Paul, E. K. The organocatalytic vinylogous aldol reaction: recent advances. *Chem. - Eur. J.* **2011**, *17*, 8770. (i) Cui, H.-L.; Chen, Y.-C. α,α-Dicyanoalkenes: versatile vinylogous nucleophiles for organic synthesis. *Chem. Commun.* **2009**, 4479. (j) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. Catalytic, enantioselective, vinylogous aldol reactions. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.

(2) Varvounis, G. Chapter 2 Pyrazol-3-ones. Part IV: Synthesis and Applications. *Adv. Heterocycl. Chem.* **2009**, *98*, 143.

(3) (a) Chauhan, P.; Mahajan, S.; Enders, D. Asymmetric synthesis of pyrazoles and pyrazolones employing the reactivity of pyrazolin-5-one derivatives. *Chem. Commun.* **2015**, *51*, 12890. (b) Liu, S.; Bao, X.; Wang, B. Pyrazolone: a powerful synthon for asymmetric diverse derivatizations. *Chem. Commun.* **2018**, *54*, 11515. (c) Carceller-Ferrer, L.; Blay, G.; Pedro, J. R.; Vila, C. Recent advances in catalytic enantioselective synthesis of pyrazolones with a tetrasubstituted stereogenic center at the 4-position. *Synthesis* **2021**, *53*, 215.

(4) (a) Rassu, G.; Zambrano, V.; Pinna, L.; Curti, C.; Battistini, L.; Sartori, A.; Pelosi, G.; Casiraghi, G.; Zanardi, F. Direct and enantioselective vinylogous Michael addition of α-alkylidenepyrazolinones to nitroolefins catalyzed by dual cinchona alkaloid thioureas. *Adv. Synth. Catal.* **2014**, *356*, 2330. (b) Yetra, S. R.; Mondal, S.; Mukherjee, S.; Gonnade, R. G.; Biju, A. T. Enantioselective synthesis of spirocyclohexadienones by NHC-catalyzed formal [3+ 3] annulation reaction of enals. *Angew. Chem., Int. Ed.* **2016**, *55*, 268. (c) Liu, J.-Y.; Zhao, J.; Zhang, J.-L.; Xu, P.-F. Quaternary carbon center forming formal [3+ 3] cycloaddition reaction via bifunctional catalysis: Asymmetric synthesis of spirocyclohexene pyrazolones. *Org. Lett.* **2017**, *19*, 1846. (d) Mondal, S.; Mukherjee, S.; Yetra, S. R.; Gonnade, R. G.; Biju, A. T. Organocatalytic enantioselective vinylogous Michael-aldol cascade for the synthesis of spirocyclic compounds. *Org. Lett.* **2017**, *19*, 4367. (e) Leng, H.-J.; Li, Q.-Z.; Zeng, R.; Dai, Q.-S.; Zhu, H.-P.; Liu, Y.; Huang, W.; Han, B.; Li, J.-L. Asymmetric construction of spiropyrazolone skeletons via amine-catalyzed [3 + 3] annulation. *Adv. Synth. Catal.* **2018**, *360*, 229. (f) Xu, J.; Hu, L.; Hu, H.; Ge, S.; Liu, X.; Feng, X. Enantioselective vinylogous Michael-aldol reaction to synthesize spirocyclohexene pyrazolones in aqueous media. *Org. Lett.* **2019**, *21*, 1632. (g) Sun, B.-B.; Zhang, J.-Q.; Chen, J.-B.; Fan, W.-T.; Yu, J.-Q.; Hu, J.-M.; Wang, X.-W. Stereoselective synthesis of spirocyclohexadiene-pyrazolones via organic base and/or hydrogen bonding assisted [3 + 3] annulation reactions. *Org. Chem. Front.* **2019**, *6*, 1842. (h) Ji, Y.-L.; Li, H.-P.; Ai, Y.-Y.; Li, G.; He, X.-H.; Huang, W.; Huang, R.-Z.; Han, B. Enantio- and diastereoselective synthesis of spiropyrazolones via an organocatalytic [1+ 2+ 3] multicomponent reaction. *Org. Biomol. Chem.* **2019**, *17*, 9217. (i) Sun, B.-B.; Chen, J.-B.; Zhang, J.-Q.; Yang, X.-P.; Lv, H.-P.; Wang, Z.; Wang, X.-W. Organo-catalyzed asymmetric cascade annulation reaction for the construction of bi-spirocyclic pyrazolone and oxindole derivatives. *Org. Chem. Front.* **2020**, *7*, 796. (j) Krishna, A. V.; Reddy, G. S.; Gorachand, B.; Ramachary, D. B. Organocatalytic asymmetric formal [3 + 3]-cycloaddition to access 2,3-diazaspiro[4.5]deca-3,6-dien-1-ones. *Eur. J. Org. Chem.* **2020**, *2020*, 6623.

(5) Yang, W.; Sun, W.; Zhang, C.; Wang, Q.; Guo, Z.; Mao, B.; Liao, J.; Guo, H. Lewis-base-catalyzed asymmetric [3+ 3] annulation reaction of Morita−Baylis−Hillman carbonates: Enantioselective synthesis of spirocyclohexenes. *ACS Catal.* **2017**, *7*, 3142.

(6) (a) Amr, F. I.; Vila, C.; Blay, G.; Muñoz, M. C.; Pedro, J. R. Organocatalytic enantioselective alkylation of pyrazol-3-ones with isatin-derived ketimines: stereocontrolled construction of vicinal tetrasubstituted stereocenters. *Adv. Synth. Catal.* **2016**, *358*, 1583. (b) Vila, C.; Amr, F. I.; Blay, G.; Muñoz, M. C.; Pedro, J. R. Organocatalytic enantioselective synthesis of pyrazoles Bearing a quaternary stereocenter. *Chem. - Asian J.* **2016**, *11*, 1532. (c) Carceller-Ferrer, L.; Vila, C.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. Organocatalytic enantioselective aminoalkylation of pyrazol-3-ones with aldimines generated *in situ* from α-amido sulfones. *Org. Biomol. Chem.* **2019**, *17*, 9859. (d) Carceller-Ferrer, L.; González del Campo, A.; Vila, C.; Blay, G.; Muñoz, M. C.; Pedro, J. R. Organocatalytic enantioselective aminoalkylation of 5-aminopyrazole derivatives with cyclic imines. *Eur. J. Org. Chem.* **2020**, *2020*, 7450. (e) Carceller-Ferrer, L.; Blay, G.; Pedro, J. R.; Vila, C. Squaramide-catalyzed enantioselective Michael addition of pyrazol-3-ones to *ortho*-quinone methides. *Lett. Org. Chem.* **2020**, *17*, 837.

(7) (a) Chauhan, P.; Chimni, S. S. Organocatalytic asymmetric synthesis of 3-amino-2-oxindole derivatives bearing a tetra-substituted stereocenter. *Tetrahedron: Asymmetry* **2013**, *24*, 343. (b) Kaur, J.; Chimni, S. S.; Mahajan, S.; Kumar, A. Stereoselective synthesis of 3-amino-2-oxindoles from isatin imines: new scaffolds for bioactivity evaluation. *RSC Adv.* **2015**, *5*, 52481. (c) Yu, J.-S.; Zhou, F.; Liu, Y.-L.; Zhou, J. A journey in the catalytic synthesis of 3-substituted 3-aminooxindoles. *Synlett* **2015**, *26*, 2491. (d) Mohammadi Ziarani, G.; Moradi, R.; Lashgari, N. Asymmetric synthesis of chiral oxindoles using isatin as starting material. *Tetrahedron* **2018**, *74*, 1323. (e) Kaur, J.; Chimni, S. S. Catalytic synthesis of 3-aminooxindoles via addition to isatin imine: an update. *Org. Biomol. Chem.* **2018**, *16*, 3328.

(8) (a) Dounay, A. B.; Overman, L. E. The asymmetric intramolecular Heck reaction in natural product total synthesis. *Chem. Rev.* **2003**, *103*, 2945. (b) Lin, H.; Danishefsky, S. J. Gelsemine: A thought-provoking target for total synthesis. *Angew. Chem., Int. Ed.* **2003**, *42*, 36. (c) Galliford, C. V.; Scheidt, K. A. Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(9) For reviews of hybrid-based drugs, see: (a) Tsogoeva, S. B. Recent progress in the development of synthetic hybrids of natural or unnatural bioactive compounds for medicinal chemistry. *Mini-Rev. Med. Chem.* **2010**, *10*, 773. (b) Decker, M. Hybrid molecules incorporating natural products: applications in cancer therapy, neurodegenerative disorders and beyond. *Curr. Med. Chem.* **2011**, *18*, 1464. (c) Sandhu, S.; Bansal, Y.; Silakari, O.; Bansal, G. Coumarin hybrids as novel therapeutic agents. *Bioorg. Med. Chem.* **2014**, *22*, 3806. (d) Vandekerckhove, S.; D'hooghe, M. Quinoline-based antimalarial hybrid compounds. *Bioorg. Med. Chem.* **2015**, *23*, 5098.

(10) (a) Doyle, A. G.; Jacobsen, E. N. Small-molecule H-bond donors in asymmetric catalysis. *Chem. Rev.* **2007**, *107*, 5713. (b) Connon, S. Organocatalysis mediated by (thio)urea derivatives. *Chem. - Eur. J.* **2006**, *12*, 5418. (c) Alemán, J.; Parra, A.; Jiang, H.; Jørgensen, K. A. Squaramides: bridging from molecular recognition to bifunctional organocatalysis. *Chem. - Eur. J.* **2011**, *17*, 6890.

(11) The two diastereoisomers could be separated after column chromatography.

(12) Deruiter, J.; Carter, D. A.; Arledge, W. S.; Sullivan, P. J. Synthesis and Reactions of 4-isopropylidene-1-aryl-3-methyl-2-pyrazolin-5-ones. *J. Heterocycl. Chem.* **1987**, *24*, 149.

(13) Maruoka, H.; Hokao, M.; Masumoto, E.; Okabe, F.; Tanaka, R.; Miake, F.; Fujioka, T.; Yamagata, K. Chemical Reactivity and Application of 4-Alkylidene-3H-pyrazol-3-ones: Synthesis and Antifungal Activity of Polysubstituted Pyrazoles. *Heterocycles* **2016**, *93*, 362.

https://doi.org/10.1021/acs.orglett.1c02571
Org. Lett. 2021, 23, 7391−7395