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# Enantioselective Synthesis of Pyrazolo[3,4-*b*]pyridone Derivatives with Antifungal Activities against *Phytophthora capsici* and *Colletotrichum fructicola*

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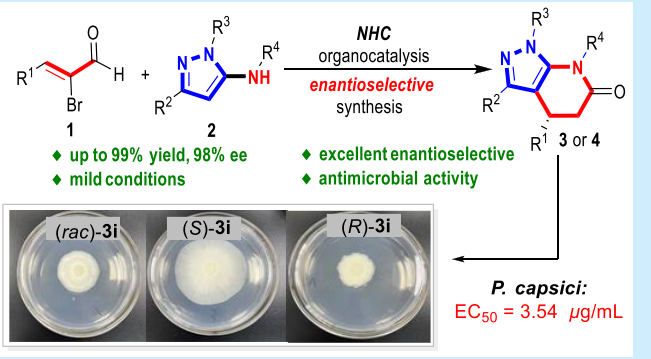
**ABSTRACT:** A chiral NHC-catalyzed [3 + 3] cycloaddition reaction is developed for the efficient synthesis of pyrazolo[3,4-*b*]pyridones in generally excellent yields and optical purities. The *R*, *S*, and racemic forms of these molecules are systematically studied via *in vitro* tests that detect antifungal activity against *Phytophthora capsici* and *Colletotrichum fructicola*. Chiral compounds (*R*)-**3i**, (*R*)-**3j**, and (*R*)-**3p** are identified to have excellent inhibitory effects against *P. capsici* and *C. fructicola*.






Pyrazolo[3,4-*b*]pyridones are heteroatom-rich structures and have been extensively used in the development of agrochemicals and pharmaceuticals (Figure 1a).[1] For instance, compound **A** containing a pyrazolo[3,4-*b*]pyridone fragment exhibited excellent insecticidal activity against *Sitophilus oryzae*.[1a] Recently discovered new JAK1-selective kinase inhibitor **B** with a pyrazolo[3,4-*b*]pyridone core was employed as the starting material for the synthesis of highly subtype-selective JAK1 inhibitors.[1f] Pyrazolo[3,4-*b*]pyridone derivative **C** exhibited excellent antiviral activity and is a promising cure for dengue fever.[1b] Therefore, the development of highly efficient and enantioselective methods for the construction of pyrazolo[3,4-*b*]pyridone derivatives is urgently needed.

N-Heterocyclic carbene (NHC), regarded as an analogue of vitamin B1, can achieve a unique catalytic activation mode and many reaction types.[2] The α-bromo enals have been used as effective precursors to generate α,β-unsaturated acylazoliums **II**[3] through various NHC organic catalysts. Significant achievements have been realized in the development of asymmetric [3 + 3], [3 + 2], and [3 + 4] cycloaddition reactions between α-bromo enals and dinucleophilic starting materials through the NHC-catalyzed LUMO activation pathway (Figure 1b).[4] However, to the best of our knowledge, the possibility that this methodology could be used to construct pyrazolo[3,4-*b*]pyridone derivatives possessing good fungicidal bioactivities has not been disclosed.

Herein, we design a series of chiral pyrazolo[3,4-*b*]pyridone derivatives for antifungal investigation against *Phytophthora capsici*[5] and *Colletotrichum fructicola*[6] for pepper protection. The optically enriched chiral pyrazolo[3,4-*b*]pyridone molecules could be quickly and enantioselectively synthesized through the NHC-catalyzed enantioselective cycloaddition reaction, with the inexpensive and readily available α-bromo enals **1** and pyrazoles **2** used as the starting materials (Figure 1c).

Initially, bromocinnamaldehyde **1a** and 5-aminopyrazole **2a** were chosen to optimize the reaction conditions (Table 1). Various NHC precatalysts were examined using $Cs_2CO_3$ as the base in THF (Table 1, entries 1−5). NHC precatalyst **A**[7] bearing an electron-rich mesityl group could give chiral pyrazolo[3,4-*b*]pyridone product **3a** in a promising yield with an excellent enantioselectivity (entry 1). When the *N*-Mes group was switched to an *N*-Ph or *N*-$C_6H_2Cl_3$ group, only a trace of the corresponding product **3a** was observed (entry 2 or 3, respectively). NHC precatalyst **D**[8] bearing a $NO_2$ group leads to a much lower enantioselectivity (entry 4). To our delight, the product yield and enantioselectivity were all significantly improved using NHC precatalyst **E**[9] for this transformation (entry 5). Then, catalyst **E** was used for the catalytic process to screen various solvents. Most of the solvents led to unsatisfactory yields or enantioselectivities (entries 6−8). Pyrazolo[3,4-*b*]pyridone product **3a** could be

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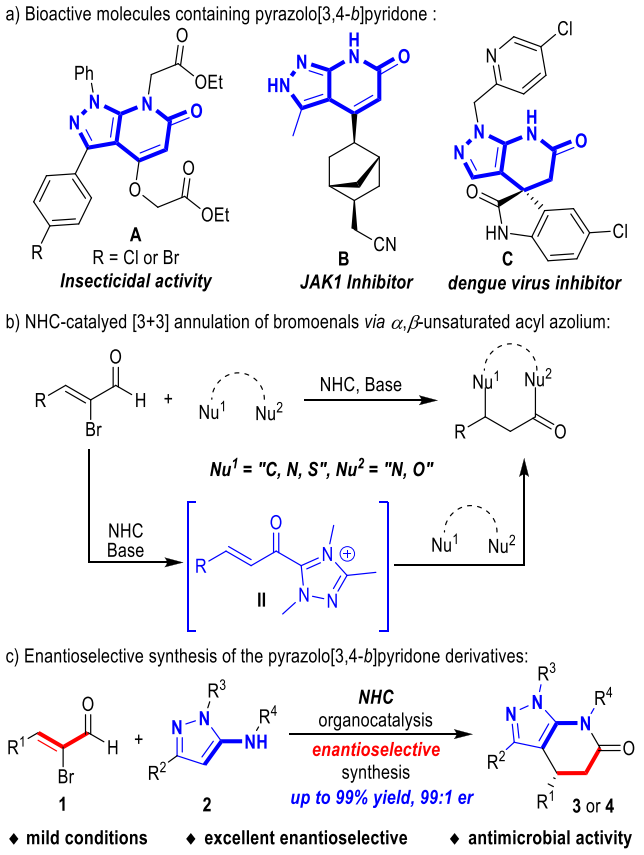
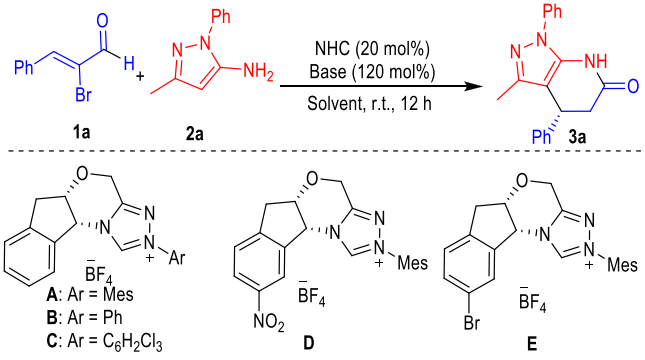



**Figure 1.** Bioactive molecules containing pyrazolo[3,4-*b*]pyridone and our project design.

obtained in 94% yield and 98% ee when EtOAc was used as the solvent. (entry 9). Changing $Cs_2CO_3$ to other bases led to lower product yields (entries 10−12). Finally, only 5% of catalyst **E** was used for this catalytic process, and the pyrazolo[3,4-*b*]pyridone product could be obtained in 96% yield and 98% ee (entry 13).

With an optimized reaction condition in hand, the substitutions and substituted patterns of *α*-bromo enals **1** were explored for reaction with substrate **2a** (Scheme 1). Regardless of the electronic property of the substituents installed at the *para* position of the benzene ring of enal **1**, the desired products could be obtained in good to excellent yields and excellent enantioselectivities (**3b−3g**). When the dimethylamino group was placed at the *para* position of the phenyl group, the product yield decreased (**3h**). 3-F and 3-Br groups on the phenyl group led to decreases in the product yields without erosion of the product optical purities (**3i** and **3k**, respectively). In contrast, the 3-Cl group on the phenyl group gave the pyrazolo[3,4-*b*]pyridone products in quantitative yield with an excellent optical purity (**3j**). When electron-withdrawing groups were installed at the *ortho* position of the phenyl group, all of the corresponding products could be formed in good to excellent yields with excellent er values (**3l−3o**). When the 2-$OCH_3$ group was placed on the phenyl ring, chiral pyrazolo[3,4-*b*]pyridone product **3p** could be produced in excellent yield and er. Switching of the phenyl group of enal **1a** to a 2-furyl group could give the desired product **3q** in 44% yield without erosion of the product optical purity. Meanwhile, switching the phenyl ring of enal substrate **1a** to a 2-naphthyl group could give the corresponding product **3r** in excellent

**Table 1. Optimization of the Reaction Conditions**[a]




| entry | NHC | base | solvent | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | **A** | $Cs_2CO_3$ | THF | 68 | 96 |
| 2 | **B** | $Cs_2CO_3$ | THF | <5 | – |
| 3 | **C** | $Cs_2CO_3$ | THF | <5 | – |
| 4 | **D** | $Cs_2CO_3$ | THF | 77 | 18 |
| 5 | **E** | $Cs_2CO_3$ | THF | 85 (86) | 98 |
| 6 | **E** | $Cs_2CO_3$ | DCM | 99 | 92 |
| 7 | **E** | $Cs_2CO_3$ | toluene | 80 | 82 |
| 8 | **E** | $Cs_2CO_3$ | $CH_3CN$ | 12 | 82 |
| 9 | **E** | $Cs_2CO_3$ | EtOAc | 95 (94) | 98 |
| 10 | **E** | DBU | EtOAc | 60 | 96 |
| 11 | **E** | $Et_3N$ | EtOAc | 82 | 96 |
| 12 | **E** | DMAP | EtOAc | 65 | 96 |
| 13[d] | **E** | $Cs_2CO_3$ | EtOAc | 98 (96) | 98 |

[a]General conditions (unless otherwise specified): bromocinnamaldehyde **1a** (0.05 mmol), 5-aminopyrazole **2a** (0.05 mmol), NHC catalyst (0.01 mmol), and base (0.06 mmol) in 1.0 mL of solvent at r.t. for 12 h. [b]Determined by $^1$H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields based on **2a** are given in parentheses. [c]ee determined via UPLC on a chiral stationary phase. [d]**1a** (0.24 mmol), **2a** (0.20 mmol), **E** (0.01 mmol), and $Cs_2CO_3$ (0.24 mmol) in EtOAc (3.0 mL) at r.t. for 12 h.

yield and er. Notably, the aliphatic enal could also be used in this transformation, and the corresponding product **3s** could also be produced in good yield and enantioselectivity under the current reaction condition. Increasing the length of the carbon chains of aliphatic *α*-bromo enals **1** did not affect the reaction enantioselectivities, although the product yields were obviously decreased in these cases (**3t−3w**).

Then, the scope of pyrazole substrates **2** was also examined (Scheme 2). Electron-donating substitutions at position 3 on the pyrazole ring of substrate **2** proved to be crucial for this transformation, because chiral pyrazolo[3,4-*b*]pyridone product **4a** could be formed in only 36% yield under the currently optimized reaction condition. Replacing the methyl group installed on pyrazole **2a** with various aliphatic groups could lead to the formation of the corresponding products in moderate yields and excellent er values (**4b−4d**). When this methyl group was replaced with a phenyl group, pyrazolo[3,4-*b*]pyridone product **4e** could be obtained in quantitative yield without erosion of the product er value. Substituents with different electronic properties could be installed at the *para* and *ortho* positions of the phenyl group of **2a**, with all of the target products formed in excellent enantioselectivities (**4f−4i**). Replacing the phenyl ring on **2a** with a methyl group led to the formation of product **4j** in excellent yield with little erosion of the er. Note that the pyrazole ring of **2a** could be switched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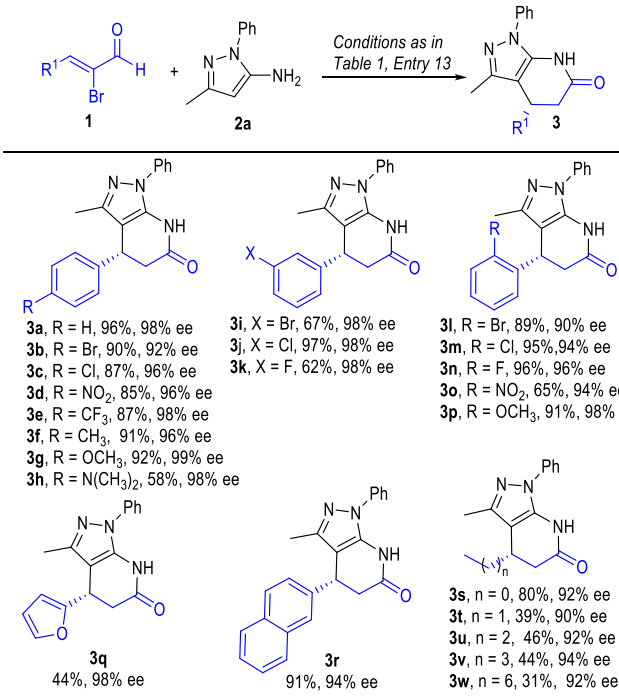
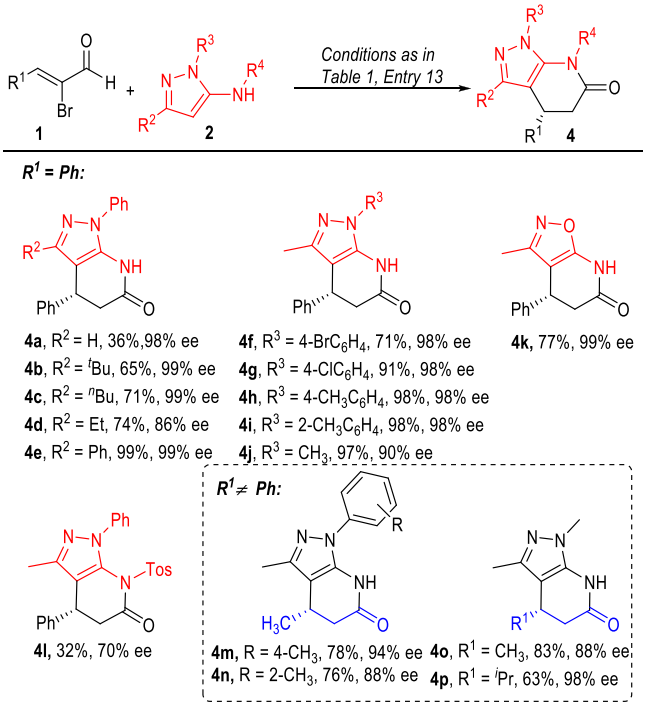
**Scheme 1. Scope of α-Bromo Enals 1**[a]




[a]Reaction conditions as in entry 13 of Table 1: α-bromo enals **1** (0.24 mmol), substrate **2a** (0.20 mmol), NHC catalyst **E** (0.01 mmol), and $Cs_2CO_3$ (0.24 mmol) in EtOAc (3.0 mL) at r.t. for12 h. Yields are isolated yields. er values were obtained from HPLC or UPLC analysis via a chiral stationary phase.

**Scheme 2. Scope of Substrates 2**[a]




[a]Reaction conditions as in entry 13 of Table 1: α-bromo enals **1** (0.24 mmol), substrate **2** (0.20 mmol), NHC catalyst **E** (0.01 mmol), and $Cs_2CO_3$ (0.24 mmol) in EtOAc (3.0 mL) at r.t. for 12 h. Yields are isolated yields. er values were obtained from HPLC or UPLC analysis via a chiral stationary phase.

to an isoxazole ring to afford product **4k** in good yield as a single enantiomer. Protecting the amino group of substrate **2a** with a Ts group led to significant erosion in either the product yield or the enantioselectivity of **4l**. It is worth noting that aliphatic α-bromo enals could also react well with substituted 5-aminopyrazole derivatives, and the corresponding pyrazolo-[3,4-*b*]pyridone products could be formed in moderate to good yields and good to excellent ee values (**4m**−**4p**).

Additionally, the carbonyl group of **3a** could be reduced to generate compound **5** in moderate yield with an excellent enantioselectivity, and the free amino group of **3a** could react with BnBr to give compound **6** in 74% yield and 99:1 er (Figure 2).

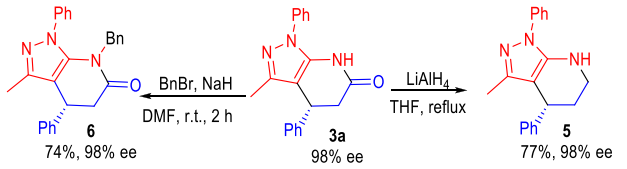



**Figure 2.** Transformations of pyrazolo[3,4-*b*]pyridone **3a**.

Meanwhile, a possible reaction mechanism for this transformation is described (Figure 3). α-Bromo enal substrate **1a**

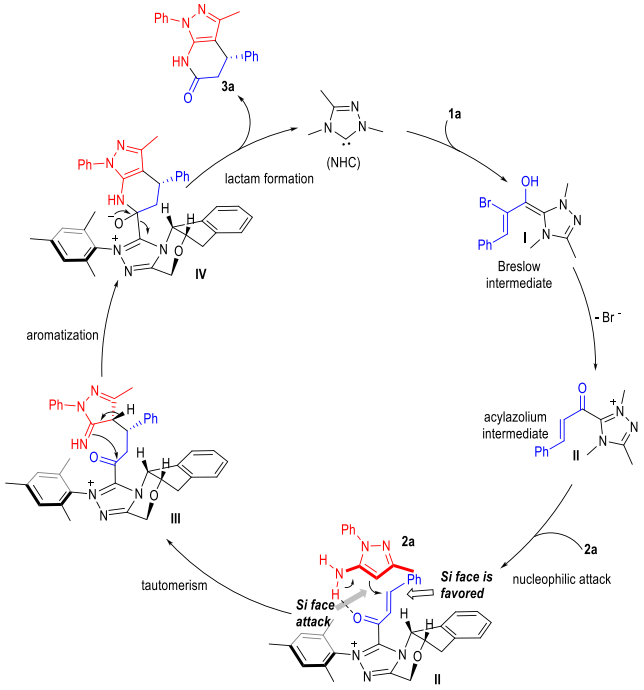



**Figure 3.** Proposed reaction mechanism for the enantioselective construction of the chiral pyrazolo[3,4-*b*]pyridone.

could be activated by the NHC catalyst to generate Breslow intermediate **I**.[10] α,β-Unsaturated acyl azolium intermediate **II**[3,11] derived from intermediate **I** then reacts with nucleophilic substrate **2a**. The *re* face of the nucleophilic 4-C($sp^2$) group of **2a** could preferentially attack the *si* face of the β-C($sp^2$) group of acyl azolium intermediate **II** to generate intermediate **III**.[4h] Intermediate **III** then goes through an intramolecular lactam formation process to give pyrazolo[3,4-*b*]pyridone product **3a**.

A series of racemic compounds were synthesized from α-bromo enal **1** and pyrazole substrates **2**, and their antifungal



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activities against plant pathogens *P. capsici* and *C. fructicola* were evaluated by the mycelium growth rate test (Table 2).

**Table 2. *In Vitro* Antimicrobial Activity**

| | inhibition rate (%) (50 μg/mL) | |
|---|---|---|
| compound | *P. capsici* | *C. fructicola* |
| (*rac*)-**3b** | 30.98 ± 0.83 | 47.41 ± 1.25 |
| (*rac*)-**3i** | 65.39 ± 0.19 | 51.25 ± 0.59 |
| (*rac*)-**3j** | 65.32 ± 0.18 | 52.36 ± 0.77 |
| (*rac*)-**3k** | 14.98 ± 0.78 | 29.34 ± 0.49 |
| (*rac*)-**3n** | 18.43 ± 0.26 | 29.98 ± 1.41 |
| (*rac*)-**3p** | 36.65 ± 0.24 | 55.15 ± 0.10 |
| (*rac*)-**3q** | 32.21 ± 0.35 | 29.70 ± 0.71 |
| (*rac*)-**3r** | 36.44 ± 0.13 | 22.00 ± 0.72 |
| (*rac*)-**4b** | 31.27 ± 0.54 | 39.65 ± 0.54 |
| (*rac*)-**4d** | 39.76 ± 0.67 | 12.55 ± 0.80 |
| (rac)-**4g** | 37.84 ± 0.18 | 26.36 ± 0.51 |
| (*rac*)-**5** | 26.78 ± 0.29 | 49.18 ± 2.20 |
| azoxystrobin | 63.08 ± 1.01 | 52.80 ± 0.98 |

Commercially available pesticide azoxystrobin was used as a positive control (for more details, see the Supporting Information). The 3-Br or 3-Cl groups on the benzene ring can significantly affect the antifungal activity against *P. capsici*, with obtained inhibition rates of 65.39% and 65.32%, respectively, which are equivalent to that of the commercial fungicide azoxystrobin [(*rac*)-**3i** and (*rac*)-**3j**]. Meanwhile, compounds (*rac*)-**3i** and (*rac*)-**3j** also showed better effects on the inhibition of plant pathogen *C. fructicola* than the commercial drug azoxystrobin. The 2-$CH_3O$ group incorporated into the phenyl group exhibited a good effect against *C. fructicola* with an inhibition rate of 55.15%, which is superior to that of the commercial fungicide azoxystrobin [(*rac*)-**3p**].

It is worthwhile to discuss the relationship between the bioactivity and the chiral configuration. The enantiomers and racemic compounds of bioactive molecules **3i**, **3j**, and **3p** were synthesized using the NHC precatalysts (+)-**E**, (−)-**E**, and (±)-**F**, respectively, under otherwise identical reaction conditions. Then, the antifungal activities against *P. capsici* and *C. fructicola* of the enantiomers and racemic compounds of products **3i**, **3j**, and **3p** were evaluated at a concentration of 50 μg/mL (Table 3). The results demonstrated that the *R*-enantiomers of the target compounds possessed better antifungal activities than the *S*-enantiomers and their racemic mixtures. The $EC_{50}$ values of **3i** and **3j** were then calculated as 3.54 and 5.53 μg/mL, respectively. All of the enantiomers of **3i** and **3j** showed moderate bioactivity against *C. fructicola*. Compare with the commercial fungicide azoxystrobin, pyrazolo[3,4-*b*]pyridone products **3i** and **3j** showed better antifungal activities.

Then the inhibitory effect of compound (*R*)-**3p** against *C. fructicola* was also evaluated, with an inhibition rate of 72.31% and an $EC_{50}$ value of 5.23 μg/mL obtained. The antifungal activity of (*R*)-**3p** is comparable to that of the commercial pesticide carbendazim and is much better than that of azoxystrobin.

In summary, we have developed an NHC-catalyzed enantioselective [3 + 3] cycloaddition reaction for the construction of the bioactive pyrazolo[3,4-*b*]pyridone derivatives. A variety of substituted pyrazolo[3,4-*b*]pyridone derivatives could be formed in generally good to excellent yields with excellent enantioselectivities. Subsequently, their

**Table 3. Antimicrobial Effects of Different Configurations of Compounds 3i, 3j, and 3p and $EC_{50}$ Values**

(a) Antimicrobial Effect of Different Configurations of Compounds **3i**, **3j**, and **3p**

| | inhibition rate (%) (50 μg/mL) | |
|---|---|---|
| compound | *P. capsici* | *C. fructicola* |
| (*rac*)-**3i** | 65.39 ± 0.17 | 51.25 ± 0.59 |
| (*R*)-**3i** | 76.07 ± 0.67 | 47.98 ± 1.33 |
| (*S*)-**3i** | 33.99 ± 0.90 | 47.92 ± 2.03 |
| (*rac*)-**3j** | 65.32 ± 0.16 | 52.36 ± 0.77 |
| (*R*)-**3j** | 78.41 ± 0.07 | 36.80 ± 1.14 |
| (*S*)-**3j** | 43.77 ± 1.55 | 54.07 ± 1.46 |
| (*rac*)-**3p** | − | 58.99 ± 0.10 |
| (*R*)-**3p** | − | 72.31 ± 0.56 |
| (*S*)-**3p** | − | 45.27 ± 2.06 |
| azoxystrobin | 63.08 ± 1.01 | 52.80 ± 0.98 |

(b) $EC_{50}$ Values of Compounds (*R*)-**3i**, (*R*)-**3j**, and (*R*)-**3p**

| compound | *R* | regression equation | $EC_{50}$ |
|---|---|---|---|
| | | *P. capsici* | |
| (*R*)-**3i** | 0.9542 | $y = 0.4876x + 4.7324$ | 3.54 |
| (*R*)-**3j** | 0.9517 | $y = 0.7123x + 4.4771$ | 5.53 |
| azoxystrobin | 0.9797 | $y = 0.7039x + 3.9622$ | 29.81 |
| | | *C. fructicola* | |
| (*R*)-**3p** | 0.9879 | $y = 0.5624x + 4.5962$ | 5.23 |
| azoxystrobin | 0.9719 | $y = 0.5224x + 4.2645$ | 25.58 |
| carbendazim | 0.9636 | $y = 0.7659x + 5.6800$ | 0.13 |

bioactivities were evaluated against *P. capsici* and *C. fructicola*, and we found that the stereoconfigurations (*R*, *S*, and *rac*) of the compounds were crucial for their antimicrobial activities. Compounds (*R*)-**3i** and (*R*)-**3j** exhibit promising antifungal activities against *P. capsici* with $EC_{50}$ values of 3.54 and 5.53 μg/mL, respectively. Compound (*R*)-**3p** has a good inhibitory effect against *C. fructicola* with an $EC_{50}$ value of 5.23 μg/mL. Further investigations of the biological activities of the chiral pyrazolo[3,4-*b*]pyridone products are currently in progress in our laboratories.

## ■ ASSOCIATED CONTENT

### Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c03945.

Experimental procedures and spectral data for all new compounds (PDF)

### Accession Codes

CCDC 2154172 contains 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.

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## Author Contributions

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## Notes

The authors declare no competing financial interest.

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