molecules

MDPI

Article

Diastereoselective Cascade Cyclization of Diazoimides with Alkylidene Pyrazolones for Preparation of Pyrazole-Fused Oxa-Bridged Oxazocines

Kuo Wang, Yue Zhang, Lu-Yu Cai, Xiu-Qing Song, Chen Wang, Jia-Rui Zhang, Yi-Fan Pan and Hong-Wu Zhao *

College of Life Science and Bio-Engineering, Beijing University of Technology, No.100 Pingleyuan, Chaoyang District, Beijing 100124, China; wk1632748255@bjut.edu.cn (K.W.); zhangyueyue@emails.bjut.edu.cn (Y.Z.); cai@emails.bjut.edu.cn (L.-Y.C.); song@bjut.edu.cn (X.-Q.S.); chenw7132@emails.bjut.edu.cn (C.W.); zhangjiarui@emails.bjut.edu.cn (J.-R.Z.); panyifan@emails.bjut.edu.cn (Y.-F.P.)

* Correspondence: hwzhao@bjut.edu.cn; Tel./Fax: +86-10-6739-6211

Abstract: Under the catalysis of $Rh_2(OAc)_4$ (10 mol%) and binapbisphosphine ligand (±)-**L3** (20 mol%) in DCE at 80 °C, the cascade cyclization of diazoimides with alkylidenepyrazolones underwent stereoselectively (dr > 20:1), affording pyrazole-fused oxa-bridged oxazocines in reasonable chemical yields. The chemical structure and relative configuration of title products were firmly identified by X-ray diffraction analysis.

Keywords: diastereoselectivity; cascade cyclization; diazoimide; alkylidenepyrazolone; oxazocine

check for updates

Citation: Wang, K.; Zhang, Y.; Cai, L.-Y.; Song, X.-Q.; Wang, C.; Zhang, J.-R.; Pan, Y.-F.; Zhao, H.-W. Diastereoselective Cascade Cyclization of Diazoimides with Alkylidene Pyrazolones for Preparation of Pyrazole-Fused Oxa-Bridged Oxazocines. *Molecules* **2023**, *28*, 7021. https://doi.org/10.3390/molecules28207021

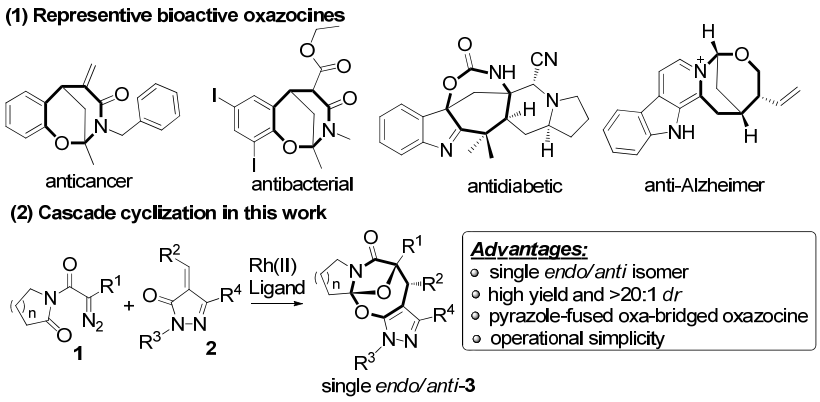
Academic Editor: Mauro Pineschi

Received: 13 September 2023
Revised: 6 October 2023
Accepted: 8 October 2023
Published: 10 October 2023

Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Oxazocines belong to a class of medicinally and biologically important chemical skeletons and have a wide range of biological activities such as anticancer, antibacterial, antidiabetic, and anti-Alzheimer properties [1,2] (Scheme 1(1)). Due to the variety of the significant bioactive potentials with oxazocine scaffolds, organic and medicinal chemists have created a variety of synthetic methodologies for their efficient and concise constructions [3–8]. Moreover, in this context, non-stereoselective and stereoselective cycloadditions have functioned as the crucial protocols for preparing a variety of structurally diverse and complex bridged and non-bridged oxazocines [9–14]. Importantly, elegant and powerful synthetic methodologies have appeared to prepare heterocycle-fused bridged oxazocines, but this area has witnessed slow development in recent years [15]. So, designing and exploring new synthetic protocols is urgently needed to obtain structurally new and unique oxa-bridged oxazocines fused with heterocyclic motifs.



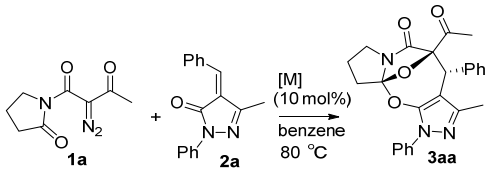
Scheme 1. Representative bioactive oxazocines and the cascade cyclization in this work.

Diazoimides constitute a kind of robust and versatile building block and they are broadly applied to prepare bioactive natural products and drug scaffolds by means of their cycloadditions [16–23]. Normally, when treated with transition metals, diazoimides can deliver structurally diverse acyclic or cyclic carbonyl ylides, enabling many types of cycloadditions with a wide range of dipolarophiles [24–30]. Primarily, the cycloaddition of cyclic carbonyl ylides derived from diazoimides with structurally various dipolarophiles can be used to more efficiently and concisely deliver oxa-bridged heterocyclic scaffolds [31–35]. On the basis of the previous advances concerning the cyclization of carbonyl yildes [36–40], we envisioned the transition-metal catalyzed novel cascade cyclization of diazoimides **1** with alkylidenepyrazolones **2**, which found a few examples of the cycloadditions centering on their enone moieties [41–44] (Scheme 1(2)). Pleasingly, in the presence of $Rh_2(OAc)_4$ (10 mol%) and binapbisphosphine ligand (±)-**L3** (20 mol%) in DCE at 80 °C, the newly designed cascade cyclization proceeded readily and diastereoselectively furnished pyrazole-fused oxa-bridged products **3** in reasonable chemical yields with excellent diastereoselectivities (>20:1 dr). Presumably, the formation of the aromatic pyrazole ring in the products substantially facilitates the cascade cyclization explored in our work. To the best of our knowledge, such a work has not been reported in the literature to date.

2. Results and Discussion

Initially, in benzene at 80 °C we scrutinized several transition-metal catalysts for their effects on the cascade cyclization of diazoimide **1a** with alkylidenepyrazolone **2a**, as described in Table 1. Generally, all the tested transition-metal catalysts provided product **3aa** with excellent diastereoselectivity (>20:1 dr). By comparison, the chemical yield of **3aa** highly depended on the screened transition-metal catalysts. In the presence of $Ru(bpy)_3Cl_2.6H_2O$, the cascade cyclization delivered product **3aa** in a trace amount (entry 1). As for catalysts $Ru(OAc)_3$ and $Rh_2(Oct)_4$, in contrast with $Ru(bpy)_3Cl_2.6H_2O$, they behaved well to provide product **3aa** in 43% chemical yield (entries 1 vs. 2 and 3). In the case of $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$, and $Rh(OAc)_3$ as catalysts, they differently increased the chemical yield of the cascade cyclization (entries 1–3 vs. 4–6). Finally, we observed that catalyst $Rh_2(OAc)_4$ acted most efficiently to furnish product **3aa** in the highest chemical yield (entries 1–6 vs. 7).

Table 1. Screening of metal-catalysts [a].



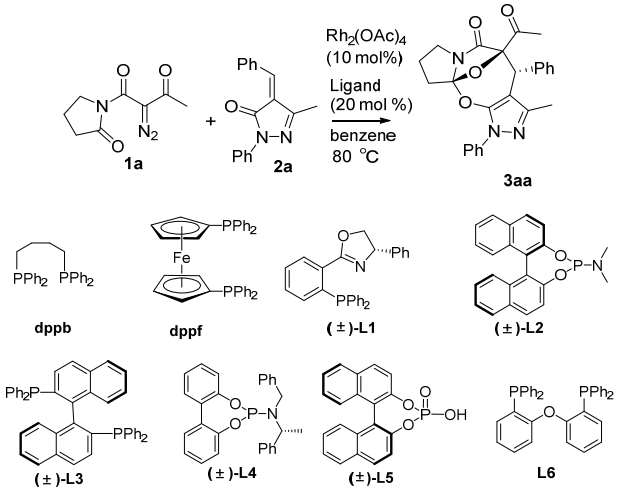
Entry	[M]	Time (h)	Yield [b] (%)	dr [c]
1	$Ru(bpy)_3Cl_2·6H_2O$	10	trace	–
2	$Ru(OAc)_3$	10	43	>20:1
3	$Rh_2(Oct)_4$	10	43	>20:1
4	$Pd_2(dba)_3$	10	66	>20:1
5	$Pd(PPh_3)_2Cl_2$	10	75	>20:1
6	$Rh(OAc)_3$	10	70	>20:1
7	$Rh_2(OAc)_4$	2.0	82	>20:1
8 [d]	$Rh_2(OAc)_4$	12	NR [e]	–

[a] Reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol) and [M] (10 mol%) in benzene (1.5 mL) at 80 °C. [b] Isolated yield. [c] Determined by ^{1}H NMR. [d] Reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol) and [M] (10 mol%) in benzene (1.5 mL) at 60 °C. [e] No reaction.

Next, together with $Rh_2(OAc)_4$ as the catalyst in benzene at 80 °C, we examined a few mono- and bisphosphine ligands to clarify their effects on the cascade cyclization of diazoimide **1a** with alkylidenepyrazolone **2a**, as depicted in Table 2. In the absence of a

ligand, the cascade cyclization generated product **3aa** in 82% chemical yield with >20:1 dr (entry 1). Regarding ligands dppf, (±)-**L1**, (±)-**L4**, and (±)-**L6**, they hugely inhibited the occurrence of the cascade cyclization and furnished product **3aa** in a trace amount after 10 h (entries 3–4, 7, and 9). Regarding ligands dppb, (±)-**L2**, and (±)-**L5**, they performed well to deliver product **3aa** in reasonable chemical yields with excellent diastereoselectivities (entries 2, 5, and 8). Lastly, we identified that ligand (±)-**L3** behaved quite efficiently to afford product **3aa** in a chemical yield of 88% (entry 6).

Table 2. Screening of mono- and bisphosphine ligands [a].

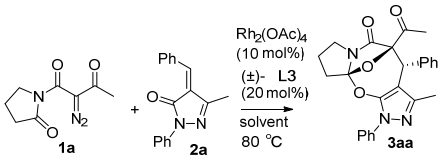


Entry	Ligand	Time (h)	Yield [b] (%)	dr [c]
1	-	2.0	82	>20:1
2	dppb	6.0	73	>20:1
3	dppf	10	trace	–
4	(±)-**L1**	10	trace	–
5	(±)-**L2**	6.0	77	>20:1
6	(±)-**L3**	1.0	88	>20:1
7	(±)-**L4**	10	trace	–
8	(±)-**L5**	1.0	78	>20:1
9	**L6**	10	trace	–

[a] Reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol), $Rh_2(OAc)_4$ (10 mol%), and ligand (20 mol%) in benzene (1.5 mL) at 80 °C. [b] Isolated yield. [c] Determined by ^1H NMR.

Moreover, with the use of $Rh_2(OAc)_4$ and (±)-**L3** at 80 °C, we examined a variety of differently polar solvents for their effects on the cascade cyclization of diazoimide **1a** with alkylidenepyrazolone **2a**, as outlined in Table 3. Generally, in the screened solvents, the cascade cyclization formed product **3aa** with excellent diastereoselectivity (>20:1 dr) (entries 1–8). However, the attempted solvents largely influenced the chemical yield of the cascade cyclization. Choosing DMF as the reaction solvent completely inhibited the occurrence of the cascade cyclization (entry 6). As for solvents HFIP and DCM, they afforded product **3aa** in a trace amount after 10 h (entries 7 and 9). Using 1,4-dioxane and THF as the reaction solvents, cascade cyclization generated product **3aa** in lower chemical yields (entries 2–3). Satisfyingly, we observed that in the aromatic solvents such as benzene, toluene, and $PhCF_3$, the [4+3] cycloaddition produced product **3aa** in reasonable chemical yields (entries 1, 4–5). In the end, we found the cascade cyclization in solvent 1,2-DCE performed very well in terms of reactivity, chemical yield, and diastereoselectivity (entry 8). So, at this point, we determined the optimal reaction conditions for the cascade cyclization, as shown below: **1a**/**2a** = 1.5:1.0 (mmol/mmol), $Rh_2(OAc)_4$ (10 mol%), (±)-**L3** (20 mol%), DCE, 80 °C.

Table 3. Screening of solvents [a].

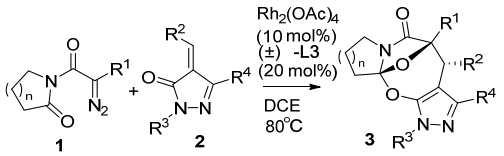


Entry	Solvent	Time (h)	Yield [b] (%)	dr [c]
1	benzene	1.0	88	>20:1
2	1,4-dioxane	5.0	22	>20:1
3	THF	5.0	35	>20:1
4	toluene	0.5	73	>20:1
5	$PhCF_3$	1.0	80	>20:1
6	DMF	10	NR [d]	–
7	HFIP	10	trace	–
8	1,2-DCE	1.0	98	>20:1
9	DCM	10	trace	–

[a] Reactions were carried out with **1a** (0.15 mmol), **2a** (0.1 mmol), $Rh_2(OAc)_4$ (10 mol%), and (±)-**L3** (20 mol%) in solvent (1.5 mL) at 80 °C. [b] Isolated chemical yield. [c] Determined by ^{1}H NMR. [d] No reaction.

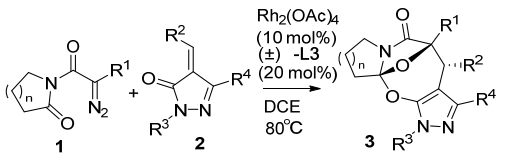
Finally, under optimal reaction conditions, we broadened the reaction scope of the cascade cyclization via diversifying substrates **1** and **2**, as summarized in Table 4. Basically, most of the explored cascade cyclizations behaved quite well in stereocontrols, and provided products **3** with excellent diastereoselectivities (>20:1 dr). By comparison, the chemical yield of the screened [4+3] cycloadditions ranged widely with the used substrates **1** and **2**. In the cascade cyclization with diazoimide **1a**, the substrates **2** with Me as the R^4 group allowed for the introduction of electron-poor or electron-rich aryls at R^2 or R^3 positions, and delivered products **3aa**–**3ag** in 65–98% chemical yields (entries 1–7). Generally, in this context, the **2** substrates bearing an electron-rich aryl as the R^2 or R^3 group acted more efficiently than the **2** substrates possessing an electron-poor aryl as the R^2 or R^3 group, and gave rise to **3** products in higher chemical yields (e.g., entries 2–3 vs. 4; 6 vs. 7). Concerning the cascade cyclization with diazoimide **1a**, alkylidenepyrazolone **2h** (where $R^2 = R^3 = R^4 = Ph$) resulted in the formation of **3ah** in 88% chemical yield (entry 8). Unfortunately, the substrates **2i** (R^2 = Ph, R^3 = Me, R^4 = Ph), **2j** (R^2 = Ph, R^3 = Me, R^4 = Me), and **2k** (R^2 = Ph, R^3 = Me, R^4 = Ph) completely failed to conduct the [4+3] cycloaddition with diazoimide **1a** (entries 9–11). So, in this series, positioning an aryl group at the R^2 position is indispensable to maintain the reactivity of the cascade cyclizations (entries 1 vs. 9; 8 vs. 9).

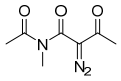
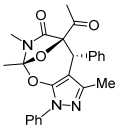
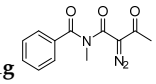
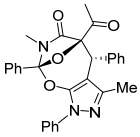
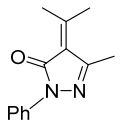
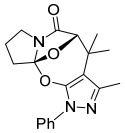
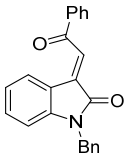
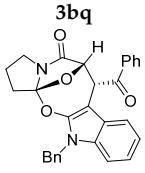
Table 4. Substrate scope [a].



Entry	1	2 (R^2, R^3, R^4)	3	Time (h)	Yield [b] (%)	dr [c]
1	**1a**	**2a** (C_6H_5, C_6H_5, Me)	**3aa**	1.0	98	>20:1
2	**1a**	**2b** (4-BrC_6H_4, C_6H_5, Me)	**3ab**	0.5	73	>20:1
3	**1a**	**2c** (4-$NO_2C_6H_4$, C_6H_5, Me)	**3ac**	0.5	65	>20:1
4	**1a**	**2d** (4-MeOC_6H_4, C_6H_5, Me)	**3ad**	1.0	82	>20:1
5	**1a**	**2e** (2-Naphthyl, C_6H_5, Me)	**3ae**	0.5	80	>20:1
6	**1a**	**2f** (C_6H_5, 4-ClC_6H_4, Me)	**3af**	0.5	72	>20:1
7	**1a**	**2g** (C_6H_5, 4-MeC_6H_4, Me)	**3ag**	1.0	80	>20:1
8	**1a**	**2h** (C_6H_5, C_6H_5, C_6H_5)	**3ah**	1.0	88	>20:1
9	**1a**	**2i** (C_6H_5, Me, C_6H_5)	**3ai**	24	NR [d]	–
10	**1a**	**2j** (C_6H_5, Me, Me)	**3aj**	24	NR [d]	–

Table 4. *Cont.*

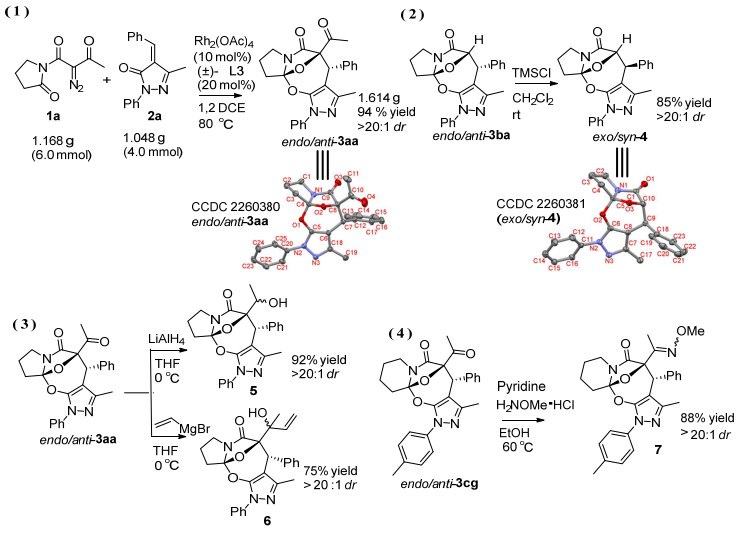


Entry	1	2 (R^2, R^3, R^4)	3	Time (h)	Yield [b] (%)	dr [c]
11	**1a**	**2k** (C_6H_5, Me, H)	**3ak**	24	NR [d]	–
12	**1b**	**2a** (C_6H_5, C_6H_5, Me)	**3ba**	0.1	77	>20:1
13	**1c**	**2a** (C_6H_5, C_6H_5, Me)	**3ca**	0.5	70	>20:1
14	**1d**	**2a** (C_6H_5, C_6H_5, Me)	**3da**	0.5	75	>20:1
15	**1e**	**2a** (C_6H_5, C_6H_5, Me)	**3ea**	0.5	82	>20:1
16	**1f** 	**2a** (C_6H_5, C_6H_5, Me)	**3fa** 	16	35	>20:1
17	**1g** 	**2a** (C_6H_5, C_6H_5, Me)	**3ga** 	24	NR [d]	–
18	**1b**	**2b** (4-BrC_6H_4, C_6H_5, Me)	**3bb**	0.1	90	>20:1
19	**1b**	**2c** (4-$NO_2C_6H_4$, C_6H_5, Me)	**3bc**	0.1	80	>20:1
20	**1b**	**2l** (3,4,5-*tri*-MeOC_6H_2, C_6H_5, Me)	**3bl**	0.1	77	>20:1
21	**1b**	**2m** (4-$CF_3C_6H_4$, C_6H_5, Me)	**3bm**	0.1	88	>20:1
22	**1b**	**2n** (2-MeOC_6H_4, C_6H_5, Me)	**3bn**	0.1	93	>20:1
23	**1b**	**2o** 	**3bo** 	0.1	95	>20:1
24	**1c**	**2c** (4-$NO_2C_6H_4$, C_6H_5, Me)	**3cc**	0.3	80	>20:1
25	**1c**	**2d** (4-MeOC_6H_4, C_6H_5, Me)	**3cd**	0.3	90	>20:1
26	**1c**	**2e** (2-Naphthyl, C_6H_5, Me)	**3ce**	1.0	95	>20:1
27	**1c**	**2f** (C_6H_5, 4-ClC_6H_4, Me)	**3cf**	1.0	80	>20:1
28	**1c**	**2g** (C_6H_5, 4-MeC_6H_4, Me)	**3cg**	1.0	84	>20:1
29	**1c**	**2l** (3,4,5-*tri*-MeOC_6H_2, C_6H_5, Me)	**3cl**	1.0	75	>20:1
30	**1c**	**2n** (2-MeOC_6H_4, C_6H_5, Me)	**3cn**	1.0	86	>20:1
31	**1c**	**2p** (2-Thienyl, C_6H_5, Me)	**3cp**	1.0	85	>20:1
32	**1d**	**2b** (4-BrC_6H_4, C_6H_5, Me)	**3db**	1.0	60	>20:1
33	**1d**	**2d** (4-MeOC_6H_4, C_6H_5, Me)	**3dd**	1.0	78	>20:1
34	**1d**	**2e** (2-Naphthyl, C_6H_5, Me)	**3de**	1.0	91	>20:1
35	**1d**	**2g** (C_6H_5, 4-MeC_6H_4, Me)	**3dg**	1.0	90	>20:1
36	**1d**	**2l** (3,4,5-*tri*-MeOC_6H_2, C_6H_5, Me)	**3dl**	1.0	82	>20:1
37	**1d**	**2n** (2-MeOC_6H_4, C_6H_5, Me)	**3dn**	1.0	81	>20:1
38	**1e**	**2d** (4-MeOC_6H_4, C_6H_5, Me)	**3ed**	1.0	85	>20:1
39	**1e**	**2l** (3,4,5-*tri*-MeOC_6H_2, C_6H_5, Me)	**3el**	1.0	90	>20:1
40	**1e**	**2n** (2-MeOC_6H_4, C_6H_5, Me)	**3en**	1.0	50	>20:1
41	**1b**	**2q** 	**3bq** 	1.0	91	>20:1

[a] Reactions were carried out with **1** (0.15 mmol), **2** (0.1 mmol), $Rh_2(OAc)_4$ (10 mol%), and (±)-**L3** (20 mol%) in DCE (1.5 mL) at 80 °C. [b] Isolated chemical yield. [c] Determined by ^{1}H NMR. [d] No reaction.

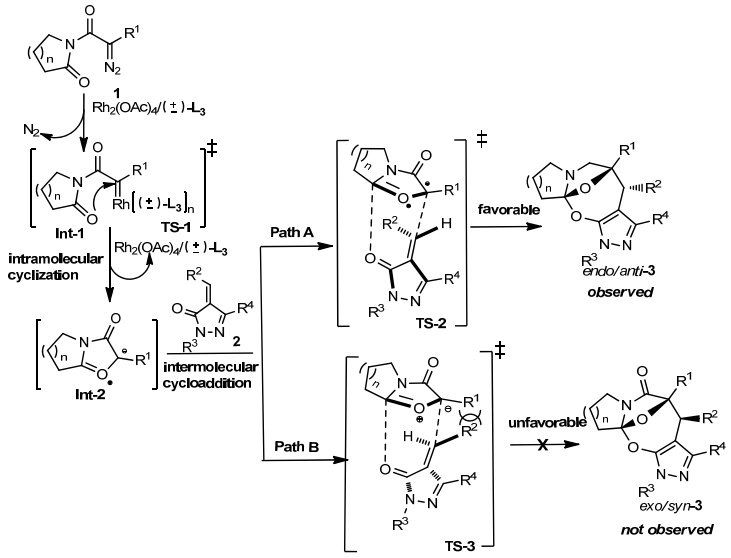
As for the cascade cyclization with alkylidenepyrazolone **2a**, substrate **1** tolerated the variation in the R^1 group and the ring size of the lactam motif, and provided products **3ba**–**3ea** in 70–82% chemical yields (entries 12–15). Basically, in this series, the **1** substrates possessing a bigger ring-sized lactam subunit commonly worked better than the **1** substrates incorporating a smaller ring-sized lactam subunit with respect to the chemical yield of the cascade cyclization (entries 13 vs. 14 vs. 15). As for substrate **1f** containing a N-methylacetamide motif, it performed poorly in the cascade cyclization with substrate **2a** and produced product **3fa** in a lower chemical yield (entry 16). Even worse, substrate **1g** bearing a N-methylbenzamide subunit failed to conduct the cascade cyclization with substrate **2a** (entry 17). Therefore, in this context, the **1** substrates containing a lactam motif generally have higher reactivities than the **1** substrates bearing a N-methylamide moiety (entries 12–15 vs. 16–17).

Moreover, with an aim of enriching the structural diversity and complexity of **3** products, we accomplished the crossed cascade cyclizations between substrates **1b**–**1e** with a broad spectrum of **2** substrates, as presented in entries 18–41 (Table 4). Apparently, in this regard, all the conducted cascade cyclizations showed excellent diastereoselectivities (>20:1 dr). In the case of the chemical yields of the cascade cyclizations, they highly depended on the selected **1** and **2** substrates and ranged widely from 50% to 95%. Mostly, the crossed cascade cyclizations behaved well, and thus delivered **3** products in moderate to high chemical yields (entries 18–39 and 41). Only the cascade cyclization between **1e** and **2n** behaved poorly, and provided product **3ej** in a quite low chemical yield (entry 40). Moreover, the oxindole-based enone **2q** reacted well with diazoimide **1b**, thus affording cycloadduct **3bl** in excellent chemical yield and diastereoselectivity (entry 41). Meanwhile, we firmly identified the chemical structure and relative stereo-configuration of the desired product **3aa** using single crystal X-ray analysis (CCDC 2260380) [45]; see details in SI) and assigned those of other title compounds by inference. In order to show the synthetic potentials of title **3** compounds, we prepared **3aa** at gram scale and completed several chemical transformations of title compounds **3ba**, **3aa,** and **3cg**, as described in Scheme 2. In the scale-up cascade cyclization, we isolated product **3aa** at a chemical yield of 94% (Scheme 2(1)). Upon treatment with TMSCl in CH_2Cl_2 at rt, compound **3ba** easily converted into its exo/syn stereoisomer **4** (CCDC 2260381) [45]; see details in Supplementary Materials) at a chemical yield of 85% (Scheme 2(2)). Furthermore, the reduction reaction of **3aa** with $LiAlH_4$ in anhydrous THF at 0 °C gave **5** at a chemical yield of 92%; and the addition reaction of **3aa** with vinylmagnesium bromide in anhydrous THF at 0 °C produced **6** at a chemical yield of 75% (Scheme 2(3)). Lastly, in the presence of pyridine in EtOH at 60 °C, the condensation reaction between **3cg** and $H_2NOMe{\cdot}HCl$ furnished **7** at a chemical yield of 88% (Scheme 2(4)).



Scheme 2. Gram-scale synthesis of **3aa** and chemical transformations of **3ba**, **3aa**, and **3cg**.

For the sake of clarifying the diastereoselective formation of product **3**, we proposed the reaction mechanism for the cascade cyclization between diazoimide **1** and alkylidenepyrazolone **2**, as illustrated in Scheme 3. Under the catalysis of $Rh_2(OAc)_4$ and (±)-**L3**, by liberating one molecule of N_2, diazoimide **1** decomposes into Rh(II)-carbenoid **Int-1**. Then, **Int-1** transforms into cyclic carbonyl ylide **Int-2** through transition state **TS-1**. Concerning **Int-2**, which was formed in situ, it can conduct the cascade cyclization with alkylidenepyrazolone **2** by adopting transition states **TS-2** or **TS-3**. In **TS-3**, there exists strong steric repulsion between R^1 and R^2 motifs; in contrast, **TS-2** fully avoids this kind of unfavorable interaction. So, **TS-2** is thermodynamically more stable than **TS-3** and mainly accounts for the formation of single endo/anti-**3**.

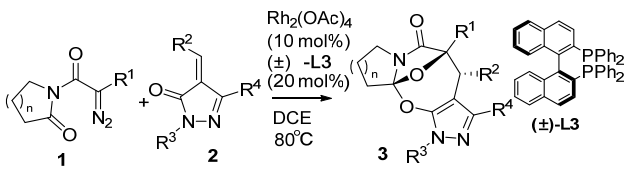


Scheme 3. Proposed mechanism for formation of product **3**.

3. Materials and Methods

Proton (^{1}H), carbon (^{13}C), and fluorine (^{19}F) NMR spectra were recorded on a Bruker Avance HD III spectrometer (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR, and 376 MHz for ^{19}F NMR) and calibrated using tetramethylsilane (TMS) as internal reference. High resolution mass spectra (HRMS) were obtained on an Agilent Technologies LC/MSD TOF spectrometer under electrospray ionization (ESI) conditions. The melting point of compounds was determined using a melting point instrument. Flash column chromatography was performed on silica gel (0.035–0.070 mm) using compressed air. X-ray single crystals were obtained on a Rigaku 002 Saturn 944 spectrometer. Thin layer chromatography (TLC) was carried out on 0.25 mm SDS silica gel coated glass plates (60F254). Eluted plates were visualized using a 254 nm UV lamp. Unless otherwise indicated, all reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before use. Diazoimides **1a**–**1g** were synthesized according to the reported procedures [10,46,47]. Alkylidenepyrazolones **2a**–**2q** were prepared according to literature procedures [48–50].

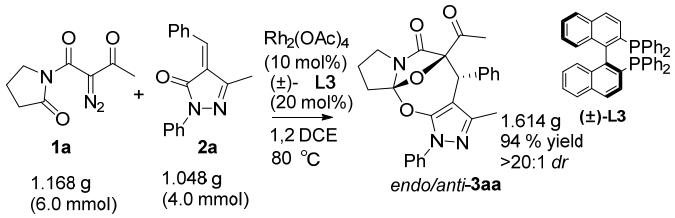
3.1. General Procedure for Cascade Cycloaddition Reaction



A mixture of diazoimides **1** (1.5 equiv, 0.15 mmol), alkylidenepyrazolones **2** (1.0 equiv, 0.1 mmol), $Rh_2(OAc)_4$ (10.0 mol%), and (±)-**L3** (20.0 mol%) in DCE (1.5 mL) was stirred

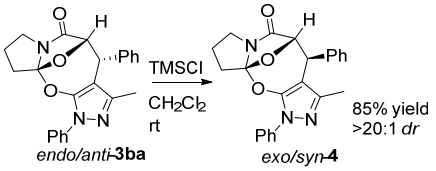
at 80 °C. After the reaction was completed as indicated by the TLC plate, the solvent was concentrated under reduced pressure and the resulting crude products were purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1~2:1) to afford **3** products (35–98% yields).

3.2. Gram-Scale Synthesis of Compound **3aa**

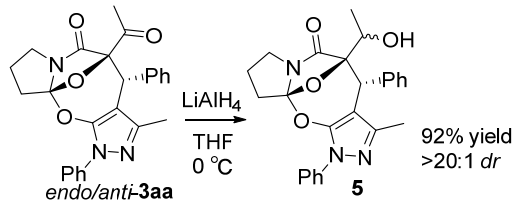


A mixture of diazoimide **1a** (1.5 equiv, 6.0 mmol, 1.168 g), alkylidenepyrazolone **2a** (1.0 equiv, 4.0 mmol, 1.048 g), $Rh_2(OAc)_4$ (10.0 mol%, 0.176 g), and (±)-**L3** (20.0 mol%, 0.497 g) in DCE (15 mL) was stirred at 80 °C. After the reaction was completed as indicated by the TLC plate, the solvent was concentrated under reduced pressure and the resulting crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 4:1) to afford product **3aa** as a white solid (1.614 g, 94% yield).

3.3. Chemical Transformations of **3ba**, **3aa**, *and* **3cg**

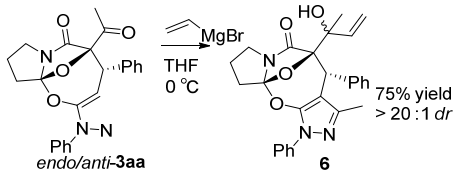


To a well-stirred solution of **3ba** (1.0 equiv, 0.1 mmol, 38.7 mg) in CH_2Cl_2 (1.0 mL), TMSCl (1.0 equiv, 0.1 mmol, 10.8 mg) was added. Then, the reaction mixture was stirred at room temperature for 12 h. After the reaction was finished as indicated by the TLC plate, the reaction mixture was concentrated under reduced pressure. The resulting reaction residue was purified using flash column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to afford product **4** as a white solid (32.8 mg, 85% yield). M.P. = 75.3–75.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.8 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.35–7.24 (m, 4H), 7.13 (d, J = 6.3 Hz, 2H), 5.69 (d, J = 1.8 Hz, 1H), 4.43 (d, J = 1.7 Hz, 1H), 3.96–3.75 (m, 2H), 2.87–2.62 (m, 2H), 2.30–2.16 (m, 2H), 2.10 (s, 3H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ171.5, 148.3, 146.6, 140.2, 138.7, 128.9, 128.8, 128.0, 127.4, 126.4, 122.7, 122.5, 121.6, 100.4, 89.1, 45.7, 41.4, 34.4, 25.0, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}N_3O_3$ 388.1656; Found 388.1655.

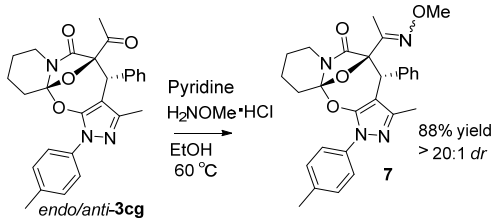


To a well-stirred solution of **3aa** (1.0 equiv, 0.1 mmol, 42.9 mg) in dry THF (1.0 mL), $LiAlH_4$ (2.0 equiv, 0.2 mmol, 7.6 mg) was added. Then, the reaction mixture was stirred at 0 °C for 1 h. After the reaction was finished as indicated by the TLC plate, the reaction mixture was concentrated under reduced pressure. The resulting reaction residue was purified using flash column chromatography on silica gel (petroleum ether/ethyl acetate = 1:1) to afford product **5** as a white solid (39.7 mg, 92% yield). M.P. = 215.7–216.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.64 (d, J = 7.8 Hz, 2H), 7.47 (d, J = 7.1 Hz, 1H), 7.44 (t, J = 7.7 Hz,

2H), 7.36–7.25 (m, 4H), 7.19 (d, *J* = 4.8 Hz, 1H), 5.15 (s, 1H), 4.03–3.91 (m, 1H), 3.77–3.67 (m, 1H), 3.41–3.29 (m, 1H), 2.60–2.47 (m, 1H), 2.41–2.25 (m, 1H), 2.25–2.12 (m, 3H) 1.51 (s, 3H), 1.13 (d, *J* = 6.3 Hz, 3H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.5, 149.1, 145.8, 138.8, 136.8, 130.6, 130.0, 128.8, 128.1, 128.0, 127.7, 126.2, 122.6, 119.1, 100.7, 94.3, 66.3, 47.3, 42.4, 35.0, 24.9, 17.9, 14.7, 14.2 ppm; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{25}H_{25}N_3O_4$ 432.1917; Found 432.1872.



To a well-stirred solution of **3aa** (1.0 equiv, 0.1 mmol, 42.9 mg) in anhydrous THF (1.0 mL), 1.0 M vinylmagnesium bromide (2.0 equiv, 0.2 mmol, 0.2 mL) was added under N_2. Then, the reaction mixture was stirred at 0 °C for 1 h. After the reaction was finished as indicated by the TLC plate, saturated NH_4Cl solution was added to quench the reaction at 0 °C. Then, the reaction mixture was extracted with ethyl acetate, and the combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the organic layers were concentrated under reduced pressure to give crude product. Finally, the crude product was purified using flash column chromatography on silica gel (petroleum ether/ethyl acetate = 2:1) to afford product **6** as a white solid (34.3 mg, 75% yield). M.P. = 92.7–93.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, *J* = 8.7, 1.2 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.28 (td, *J* = 7.4, 1.1 Hz, 3H), 7.26–7.12 (br, 3H), 6.06 (q, *J* = 10.8 Hz, 1H), 5.28 (dd, *J* = 17.3, 1.1 Hz, 1H), 5.14 (dd, *J* = 10.8, 1.2 Hz, 1H), 5.06 (s, 1H), 3.82–3.68 (m, 1H), 3.42 (s, 1H), 3.39–3.30 (m, 1H), 2.59–2.45 (m, 1H), 2.37–2.13 (m, 3H), 1.58 (s, 3H) 1.53 (s, 3H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ173.4, 149.0, 145.1, 141.1, 138.8, 138.4, 128.8, 127.2, 126.2, 122.6, 119.4, 115.2, 101.7, 92.3, 48.2, 42.4, 35.1, 25.0, 22.5, 14.3 ppm; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{27}H_{27}N_3O_4$ 458.2074; Found 458.2082.



To a well-stirred solution of **3cg** (1.0 equiv, 0.1 mmol, 45.7 mg) in dry EtOH (1.0 mL), $H_2NOMe{\cdot}HCl$ (2.0 equiv, 0.2 mmol, 16.6 mg) and pyridine (2.0 equiv, 0.2 mmol, 15.8 mg) were added. Then, the reaction mixture was stirred at 60 °C for 2 h. After the reaction was finished as indicated by the TLC plate, the reaction mixture was concentrated under reduced pressure. The resulting reaction residue was purified using flash column chromatography on silica gel (petroleum ether/ethyl acetate = 6:1) to afford product **7** as a white solid (42.7 mg, 88% yield). M.P. = 195.4–196.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.41 (d, *J* = 7.2 Hz, 2H), 7.29–7.17 (m, 5H), 4.70 (s, 1H), 3.91 (s, 3H), 3.86 (dd, *J* = 13.4, 4.4 Hz, 1H), 2.71 (d, *J* = 12.5 Hz, 1H), 2.52 (td, *J* = 12.8, 2.6 Hz, 1H), 2.39 (s, 3H), 2.04 (s, 3H), 1.96 (d, *J* = 12.7 Hz, 1H), 1.86 (td, *J* = 13.0, 4.0 Hz, 1H), 1.81–1.70 (m, 3H), 1.67 (s, 3H), 1.52–1.41 (m, 3H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ168.6, 151.3, 147.9, 145.0, 138.4, 136.2, 136.0, 130.4, 129.4, 127.8, 127.0, 122.3, 110.5, 102.4, 87.3, 62.1, 47.5, 38.7, 34.2, 23.3, 21.0, 20.9, 12.9, 11.1 ppm; HRMS (ESI-TOF) *m*/*z*: [M + H]$^+$ Calcd for $C_{28}H_{30}N_4O_4$ 487.2340; Found 487.2350.

3.4. Charaterization of 3 Products

5-acetyl-3-methyl-1,4-diphenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3aa**)*:* White solid (yield: 42.0 mg, 98%). M.P. = 152.9–153.1 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.7 Hz, 2H), 7.54–7.48 (br, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 3H), 7.28–7.25 (br, 1H)), 7.20–7.14 (br, 1H), 5.12 (s, 1H), 3.92–3.81 (m, 1H), 3.50–3.38 (m, 1H), 2.68–2.56 (m, 1H), 2.47–2.24 (m, 3H), 2.16 (s, 3H), 1.56 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 169.4, 148.9, 145.3, 138.6, 135.8, 128.8, 128.0, 127.7, 126.3, 122.6, 119.8, 100.2, 93.4, 47.5, 42.8, 35.4, 26.7, 25.0, 14.3 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{23}N_3O_4$ 430.1761; Found 430.1759.

5-acetyl-4-(4-bromophenyl)-3-methyl-1-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g] pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3ab**): White solid (yield: 37.0 mg, 73%). M.P. = 93.7–93.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.63 (d, *J* = 8.7 Hz, 2H), 7.47 (s, 1H), 7.46 (s, 2H), 7.44 (s, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 8.3 Hz, 1H), 5.12 (s, 1H), 3.93–3.84 (m, 1H), 3.47–3.38 (m, 1H), 2.67–2.56 (m, 1H), 2.46–2.25 (m, 3H), 2.59 (s, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 169.3, 148.6, 145.3, 138.5, 135.2, 131.2, 131.1, 128.8, 126.4, 122.6, 121.8, 120.0, 99.7, 93.2, 46.4, 43.0, 35.5, 26.5, 25.1, 14.4 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{22}BrN_3O_4$ 508.0866; Found 508.0867.

5-acetyl-3-methyl-4-(4-nitrophenyl)-1-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g] pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3ac**): White solid (yield: 30.8 mg, 65%). M.P. = 109.9–110.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.20 (d, *J* = 7.6 Hz, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.63 (dd, *J* = 8.7, 1.2 Hz, 2H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.36–7.27 (m, 2H), 5.30 (s, 1H), 3.92–3.86 (m, 1H), 3.49–3.42 (m, 1H), 2.67–2.62 (m, 1H), 2.48–2.34 (m, 3H), 2.21 (s, 3H), 1.58 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 197.9, 169.1, 148.2, 147.2, 145.4, 144.2, 138.4, 132.7, 130.6, 129.0, 126.7, 123.1, 122.7, 120.5, 99.2, 93.2, 46.3, 43.1, 35.5, 26.2, 25.2, 14.3ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{22}N_4O_6$ 475.1612; Found 475.1631.

5-acetyl-4-(4-methoxyphenyl)-3-methyl-1-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3ad**): White solid (yield:37.6 mg, 82%). M.P. = 87.7–88.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*7.63 (dd, *J* = 8.7, 1.2 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.82 (t, *J* = 4.4 Hz 2H), 5.06 (s, 1H), 3.90–3.83 (m, 1H), 3.80 (s, 3H), 3.45–3.39 (m, 1H), 2.65–2.58 (m, 1H), 2.42–2.31 (m, 3H), 2.16 (s, 3H), 1.58 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 198.6, 169.5, 159.0, 149.0, 145.2, 138.7, 132.5, 130.7, 128.9, 127.6, 126.3, 122.6, 119.6, 113.7, 113.1, 100.4, 93.4, 55.1, 46.9, 42.8, 35.5, 26.8, 25.0, 14.4 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{26}H_{25}N_3O_5$ 460.1867; Found 460.1864.

5-acetyl-3-methyl-4-(naphthalen-2-yl)-1-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g] pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3ae**): White solid (yield: 35.9 mg, 75%). M.P. = 168.5–168.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.89–7.68 (m, 3H), 7.51–7.47 (m, 3H), 7.48 (t, *J* = 7.4 Hz, 4H), 7.33 (t, *J* = 7.4 Hz, 2H), 5.36 (s, 1H), 3.90–3.85 (m, 1H), 3.49–3.42 (m, 1H), 2.66–2.59 (m, 1H), 2.48–2.24 (m, 3H), 2.16 (s, 3H), 1.53 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 198.6, 198.3, 169.5, 148.9, 145.4, 138.7, 132.8, 128.9, 128.1, 127.7, 127.6, 126.4, 126.1, 126.0, 122.6, 119.8, 99.8, 93.2, 47.6, 42.9, 35.5, 26.8, 25.0, 14.4 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{29}H_{25}N_3O_4$ 480.1917; Found 480.1922.

5-acetyl-1-(4-chlorophenyl)-3-methyl-4-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g] pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3af**): White solid (yield: 33.3 mg, 72%). M.P. = 143.2–143.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.60 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.51–7.47 (br, 1H), 7.41 (dt, *J* = 8.9, 2.7 Hz, 2H), 7.34–7.22 (br, 3H), 7.18–7.08 (br, 1H), 5.12 (s, 1H), 3.91–3.81 (m, 1H), 3.46–3.37 (m, 1H), 2.64–2.56 (m, 1H), 2.42–2.56 (m, 3H), 2.16 (s, 3H), 1.55 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 198.2, 169.3, 149.3, 145.4, 137.2, 135.6, 131.7, 131.5, 128.9, 128.0, 127.8, 123.6, 119.8, 100.4, 93.4, 47.4, 42.9, 35.5, 26.7, 25.0, 14.3 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{25}H_{22}ClN_3O_4$ 464.1371; Found 464.1369.

5-acetyl-3-methyl-4-phenyl-1-(p-tolyl)-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3ag**): White solid (yield: 35.4 mg, 80%). M.P. = 149.2–149.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.50 (d, *J* = 8.4 Hz, 3H), 7.36–7.26 (br, 2H), 7.26 (t, *J* = 7.8 Hz, 3H), 7.21–7.12 (br, 1H), 5.12 (s, 1H), 3.90–3.82 (m, 1H), 3.45–3.37 (m, 1H), 2.65–2.55 (m, 1H),

2.41 (s, 3H), 2.40–2.25 (m, 3H), 2.15 (s, 3H), 1.55 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.5, 169.4, 148.6, 145.3, 136.2, 135.9, 131.5, 129.7, 129.4, 128.6, 127.7, 122.7, 120.0, 100.0, 93.5, 47.6, 42.8, 35.5, 26.8, 25.0, 21.1, 14.3 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}N_3O_4$ 444.1917; Found 444.1920.

5-acetyl-1,3,4-triphenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3ah**): White solid (yield: 42.2 mg, 86%). M.P. = 76.2–76.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 5.7 Hz, 2H), 7.49 (t, J = 8.3 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.14–7.01 (m, 7H), 6.99 (d, J = 1.8 Hz, 3H), 5.39 (s, 1H), 3.90–3.82 (m, 1H), 3.48–3.39 (m, 1H), 2.67–2.55 (m, 1H), 2.46–2.25 (m, 3H), 2.14 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ198.5, 169.4, 152.0, 145.7, 138.7, 135.6, 133.7, 128.9, 128.5, 127.5, 127.4, 127.2, 126.7, 123.0, 119.9, 100.7, 93.9, 47.4, 42.9, 35.5, 26.8, 25.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{25}N_3O_4$ 492.1918; Found 492.1932.

3-methyl-1,4-diphenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3ba**): White solid (yield: 29.8 mg, 77%). M.P. = 146.8–147.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.64 (d, J = 7.9 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.40–7.32 (m, 4H), 7.30–7.26 (m, 2H), 4.78 (dd, J = 13.6, 6.6 Hz, 2H), 3.78–3.71 (m, 1H), 3.35–3.29 (m, 1H), 2.55–2.51 (m, 1H), 3.34–2.21 (m, 3H), 1.61 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 148.6, 146.5, 138.7, 135.0, 129.5, 129.5, 128.9, 128.8, 128.8, 128.5, 128.3, 128.0, 126.4, 122.7, 122.5, 120.8, 99.8, 86.1, 47.8, 42.2, 35.1, 24.8, 14.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{23}H_{21}N_3O_3$ 388.1656; Found 388.1622.

5-acetyl-3-methyl-1,4-diphenyl-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo[4,3-g]pyrido[2,1-b][1,3]oxazocin-6(1H)-one (**3ca**): White solid (yield: 31.0 mg, 70%). M.P. = 213.7–213.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 7.6 Hz, 2H), 7.16 (t, J = 7.6 Hz, 2H), 7.35–7.21 (m, 6H), 4.80 (s, 1H), 3.89 (dd, J = 13.3, 4.6 Hz, 1H), 2.76 (d, J = 12.8 Hz, 1H), 2.55 (td, J = 12.9, 3.0 Hz, 1H), 2.00–1.95 (br, 1H), 1.99 (s, 3H), 1.93 (s, 3H), 1.90–1.83 (m, 1H), 1.82–1.70 (m, 2H), 1.53–1.39 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 165.5, 148.3, 145.1, 138.3, 136.7, 129.7, 128.9, 128.4, 127.7, 126.6, 122.4, 110.4, 101.2, 91.9, 48.0, 38.9, 34.4, 27.4, 23.3, 20.8, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{25}N_3O_4$ 444.1918; Found 444.1872.

5-acetyl-3-methyl-1,4-diphenyl-4,5,9,10,11,12-hexahydro-8H-5,12a-epoxyazepino[2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3da**): White solid (yield: 34.2 mg, 75%). M.P. = 195.0–195.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 7.7 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.34–7.21 (m, 6H), 4.79 (s, 1H), 3.85 (d, J = 13.9 Hz, 1H), 2.90–2.79 (m, 2H), 2.40–2.31 (m, 1H), 1.98 (s, 3H), 1.96 (s, 3H) 1.94–1.85 (m, 2H), 1.78–1.69 (br, 1H), 1.53–1.33 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 166.4, 148.1, 145.3, 138.4, 136.9, 129.6, 128.9, 128.4, 127.7, 126.5, 122.5, 115.4, 100.8, 91.6, 48.0, 40.5, 38.4, 29.5, 28.5, 27.6, 22.5, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{27}N_3O_4$ 458.2074; Found 458.2039.

5-acetyl-3-methyl-1,4-diphenyl-4,5,8,9,10,11,12,13-octahydro-5,13a-epoxyazocino[2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3ea**): White solid (yield: 38.6 mg, 82%). M.P. = 149.5–149.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 7.7 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.34–7.21 (m, 6H), 4.80 (s, 1H), 3.70 (dt, J = 14.3, 4.0 Hz, 1H), 2.80 (td, J = 11.9, 3.6 Hz, 1H), 2.66 (dt, J = 16.1, 4.4 Hz, 1H), 2.50 (td, J = 10.8, 4.4 Hz, 1H), 1.98 (s, 3H), 1.96 (s, 3H), 1.86–1.75 (m, 3H), 1.70–1.55 (m, 3H), 1.53–1.35 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 167.0, 148.2, 145.2, 138.5, 136.8, 129.6, 128.9, 128.4, 127.7, 126.4, 122.3, 114.1, 100.9, 91.4, 48.4, 40.4, 31.7, 27.6, 27.0, 25.0, 23.8, 22.1, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{29}N_3O_4$ 472.2230; Found 472.2236.

5-acetyl-3,7,8-trimethyl-1,4-diphenyl-4,5,7,8-tetrahydro-5,8-epoxypyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3fa**): White solid (yield: 14.6 mg, 35%). M.P. = 192.5–192.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, J = 8.7, 1.2 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.38–7.25 (m, 6H), 4.80 (s, 1H), 2.76 (s, 3H), 2.09 (s, 3H), 1.98 (s, 3H), 1.93 (s, 3H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.2, 167.3, 148.2, 145.1, 138.3, 136.7, 129.7, 129.0, 128.4, 127.7, 126.6, 122.4, 112.5, 101.0,

91.8, 48.1, 27.3, 25.9, 23.0, 12.9 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{24}H_{23}N_3O_4$ 418.1761; Found 418.1767.

4-(4-bromophenyl)-3-methyl-1-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3bb**): White solid (yield: 41.8 mg, 90%). M.P. = 106.6–106.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.63 (d, *J* = 7.8 Hz, 2H), 7.53 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.50–7.41 (m, 3H), 7.31 (d, *J* = 7.4 Hz, 1H), 7.25 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.15 (dd, *J* = 8.4, 2.1 Hz, 1H), 4.74 (dd, *J* = 14.9, 6.6 Hz, 2H), 3.78–3.69 (m, 1H), 3.35–3.27 (m, 1H), 2.57–2.45 (m, 1H), 2.36–2.21 (m, 3H), 1.63 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.8, 148.3, 146.5, 138.6, 134.2, 131.7, 131.6, 131.3, 131.0, 128.9, 126.5, 122.7, 122.0, 120.9, 99.3, 85.7, 47.2, 42.2, 35.0, 26.9, 24.8, 15.0 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{23}H_{20}BrN_3O_3$ 466.0760; Found 466.0769.

3-methyl-4-(4-nitrophenyl)-1-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3bc**): White solid (yield: 34.5 mg, 80%). M.P. = 122.3–122.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.28 (dd, *J* = 8.3, 2.2 Hz, 1H), 8.20 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.56 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.46 (t, *J* = 7.4 Hz, 3H), 7.33 (t, *J*, =; 74Hz, 1H), 4.93 (d, *J* = 6.6 Hz, 1H), 4.77 (d, *J* = 6.6 Hz, 1H), 3.80–3.69 (m, 1H), 3.38–3.27 (m, 1H), 2.57–2.45 (m, 1H), 2.36–2.21 (m, 3H), 1.62 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.2, 159.2, 148.7, 146.4, 138.7, 130.6, 130.5, 129.0 128.9 128.8, 127.0, 126.3, 122.7, 122.4, 120.7, 114.1, 113.8, 113.8, 100.1, 86.2, 55.2, 47.0, 42.1, 35.0, 24.8, 14.9 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{23}H_{20}N_4O_5$ 433.1506; Found 433.1510.

3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3bl**): White solid (yield: 36.7 mg, 77%). M.P. = 89.7–90.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.63 (d, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.30 (d, *J* = 7.4 Hz, 1H), 6.54 (dd, *J* = 28.8, 1.6, Hz, 2H), 4.73 (d, *J* = 6.0 Hz, 1H), 4.65 (d, *J* = 6.0 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.78 (s, 3H), 3.76–3.69 (m, 1H), 3.39–3.30 (m, 1H), 2.54–2.48 (m, 1H), 2.35–2.20 (m, 3H), 1.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.2, 153.3, 153.0 148.6, 146.5, 138.7, 137.7, 130.6, 128.8, 126.4, 122.6, 122.4, 120.6, 107.1, 106.8, 100.0, 86.0 61.0, 56.4, 56.2, 48.3, 42.3, 35.0, 24.9, 14.8 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{26}H_{27}N_3O_6$478.1972; Found 478.1980.

3-methyl-1-phenyl-4-(4-(trifluoromethyl)phenyl)-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3bm**): White solid (yield: 40.0 mg, 88%). M.P. = 168.7–168.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.70 -7.56 (m, 4H),7.52–7.42 (m, 3H), 7.40 (d, *J* = 8.2 Hz, 1H), 7.32 (t, *J* = 7.4 Hz, 1H), 4.87 (d, *J* = 6.6 Hz, 1H), 4.76 (d, *J* = 6.6 Hz, 1H), 3.80–3.69 (m, 1H), 3.39–3.28 (m, 1H), 2.57–2.48 (m, 1H), 2.35–2.20 (m, 3H), 1.60 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 170.6, 148.1, 146.6, 139.3, 138.6, 130.3, 130.0, 130.0, 129.7, 128.9, 126.6, 125.6, 125.3, 125.3, 122.8, 121.0, 99.0, 85.7, 47.6, 42.2, 35.0, 26.9, 24.8, 15.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* 62.4 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{24}H_{20}F_3N_3O_3$ 456.1529; Found 456.1534.

4-(2-methoxyphenyl)-3-methyl-1-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3bn**): White solid (yield: 38.7 mg, 93%). M.P. = 158.2–158.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*7.66 (d, *J* = 7.6 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.34–7.26 (m, 2H), 7.18 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 2H), 5.35 (d, *J* = 7.0 Hz, 1H), 4.91 (d, *J* = 7.0 Hz, 1H), 3.93 (s, 3H), 3.78–3.65 (m, 1H), 3.35–3.27 (m, 1H), 2.57–2.46 (m, 1H), 2.35–2.17 (m, 3H), 1.69 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 171.5, 156.8, 148.6, 146.9, 138.9, 130.5, 129.5, 128.8, 128.5, 126.2, 123.1, 122.6, 122.4, 122.3, 121.6, 120.9, 120.6, 120.4, 110.1, 99.7, 87.0, 84.1, 55.4, 42.1, 39.4, 35.2, 24.8, 14.7 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{24}H_{23}N_3O_4$ 418.1761; Found 418.1763.

3,4,4-trimethyl-1-phenyl-4,5,9,10-tetrahydro-8H-5,10a-epoxypyrazolo[4,3-g]pyrrolo[2,1-b][1,3]oxazocin-6(1H)-one (**3bo**): White solid (yield: 32.2 mg, 95%). M.P. = 94.4–94.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): *δ*7.54 (dd, *J* = 8.7, 1.2 Hz, 2H), 7.40 (t, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 1H), 4.25 (s, 1H), 3.77–3.56 (m, 1H), 3.30–3.06 (m, 1H), 2.50–2.40 (m, 1H), 2.37 (s,

3H), 2.29–2.17 (m, 3H), 1.57 (s, 3H), 1.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 146.9, 144.7, 138.6, 128.7, 126.4, 123.0, 120.0, 105.9, 92.2, 41.5, 39.5, 34.4, 28.6, 24.9, 22.1, 16.5 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{21}N_3O_3$ 340.1656; Found 340.1660.

5-acetyl-3-methyl-4-(4-nitrophenyl)-1-phenyl-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo[4,3-g] pyrido[2,1-b][1,3]oxazocin-6(1H)-one (**3cc**): White solid (yield: 39.0 mg, 80%). M.P. = 231.6–231.9 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.7 Hz, 2H), 7.66 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.7 Hz, 2H), 7.47 (t, J = 7.7 Hz, 2H), 7.34 (t, J = 7.4 Hz, 1H), 4.95 (s, 1H), 3.91 (dd, J = 13.2, 4.5 Hz, 1H), 2.79 (d, J = 13.2 Hz, 1H), 2.56 (td, J = 13.0, 3.0 Hz, 1H), 2.03 (d, J = 13.5 Hz, 1H), 1.98 (s, 6H), 1.91 (dd, J = 13.3, 4.1 Hz, 1H), 1.86–1.68 (m, 2H), 1.56–1.42 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 164.9, 147.9, 147.4, 145.2, 144.5, 138.0, 130.8, 129.0, 126.9, 123.5, 122.5, 110.8, 100.2, 91.5, 46.8, 39.2, 34.4, 27.2, 23.2, 20.8, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}N_4O_6$ 489.1768; Found 489.1773.

5-acetyl-4-(4-methoxyphenyl)-3-methyl-1-phenyl-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo[4,3-g]pyrido[2,1-b][1,3]oxazocin-6(1H)-one (**3cd**): White solid (yield: 42.5 mg, 90%). M.P. = 155.4–155.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 5.8 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 7.23 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.76 (s, 1H), 3.87 (dd, J = 13.3, 4.6 Hz, 1H), 3.77 (s, 3H), 2.75 (d, J = 13.2 Hz, 1H), 2.55 (td, J = 13.0, 3.0 Hz, 1H), 2.03–1.99 (m, 1H), 1.98 (s, 3H), 1.94 (s, 3H), 1.86 (dd, J = 13.3, 4.1 Hz, 1H), 1.82–1.67 (m, 2H), 1.52–1.41 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 165.5, 158.9, 148.3, 145.0, 138.3, 130.7, 128.9, 128.8, 126.5, 122.4, 113.7, 110.3, 101.4, 92.0, 55.2, 47.3, 38.9, 34.4, 27.5, 23.2, 20.8, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{27}N_3O_5$ 474.2023; Found 474.2032.

5-acetyl-3-methyl-4-(naphthalen-2-yl)-1-phenyl-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo[4,3-g]pyrido[2,1-b][1,3]oxazocin-6(1H)-one (**3ce**): White solid. (yield: 46.8 mg, 95%). M.P. = 202.2–202.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 -7.78 (m, 2H), 7.77 (t, J = 4.5 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.52–7.45 (m, 5H), 7.33 (t, J = 7.4 Hz, 1H), 5.00 (s, 1H), 3.93 (dd, J = 13.3, 4.6 Hz, 1H), 2.81 (d, J = 13.2 Hz, 1H), 2.60 (td, J = 13.0, 3.0 Hz, 1H), 2.06–2.01 (m, 1H), 2.00 (s, 3H), 1.92 (s, 3H), 1.89 (d, J = 3.8 Hz, 1H), 1.86–1.74 (m, 2H), 1.55–1.43 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 165.5, 148.4, 145.2, 138.3, 134.3, 133.0, 132.8, 129.0, 128.8, 128.2, 128.1, 127.6, 127.4, 126.6, 126.2, 126.1, 122.4, 110.5, 101.2, 92.1, 48.0, 39.0, 34.5, 27.5, 23.3, 20.9, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{27}N_3O_4$ 494.2074; Found 494.2079.

5-acetyl-1-(4-chlorophenyl)-3-methyl-4-phenyl-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo[4,3-g] pyrido[2,1-b][1,3]oxazocin-6(1H)-one (**3cf**): White solid (yield: 38.1 mg, 80%). M.P. = 113.3–113.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 8.8 Hz, 2H), 7.33–7.22 (m, 5H), 4.80 (s, 1H), 3.89 (dd, J = 13.3, 4.6 Hz, 1H), 2.76 (d, J = 13.2 Hz, 1H), 2.52 (td, J = 13.0, 3.0 Hz, 1H), 2.08 (d, J = 13.4 Hz, 1H), 1.98 (s, 3H), 1.94 (s, 3H), 1.92–1.64 (m, 3H), 1.57–1.39 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.3, 165.4, 148.7, 145.2, 136.9, 136.5, 132.0, 129.6, 129.1, 128.4, 127.7, 123.3, 110.6, 101.5, 91.8, 48.0, 39.0, 34.4, 27.4, 23.2, 20.9, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{24}ClN_3O_4$ 478.1528; Found 478.1532.

5-acetyl-3-methyl-4-phenyl-1-(p-tolyl)-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo[4,3-g]pyrido [2,1-b][1,3]oxazocin-6(1H)-one (**3cg**): White solid (yield: 38.3 mg, 84%). M.P. = 144.7–148.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (d, J = 8.4 Hz, 2H), 7.31 (td, J = 8.5, 1.6 Hz, 2H), 7.29–7.22 (m, 5H), 4.80 (s, 1H), 3.89 (dd, J = 13.3, 4.6 Hz, 1H), 2.75 (d, J = 13.2 Hz, 1H), 2.52 (td, J = 13.0, 3.0 Hz, 1H), 2.41 (s, 3H), 2.04–1.99 (m, 1H), 1.98 (s, 3H), 1.94 (s, 3H), 1.92–1.68 (m, 3H), 1.53–1.39 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 165.5, 147.9, 145.0, 136.8, 136.4, 135.8, 129.7, 129.5, 128.3, 127.6, 122.4, 110.3, 101.0, 91.9, 48.0, 38.9, 34.4, 27.4, 23.3, 21.1, 20.8, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{27}N_3O_4$ 458.2074; Found 458.2079.

5-acetyl-3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo [4,3-g]pyrido[2,1-b][1,3]oxazocin-6(1H)-one (**3cl**): White solid (yield: 39.9 mg, 75%). M.P. = 238.3–238.7 °C;

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 7.6 Hz, 2H), 7.46 (t, J = 7.6 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 6.54 (s, 2H), 4.74 (s, 1H), 3.89 (dd, J = 13.3, 4.6 Hz, 1H), 3.83 (s, 6H), 3.82 (s, 3H), 2.74 (d, J = 13.2 Hz, 1H), 2.57 (td, J = 13.0, 3.0 Hz, 1H), 2.04 (s, 3H), 1.98 (s, 3H), 1.90 (td, J = 13.1, 3.9 Hz, 1H), 1.85–1.66 (m, 1H),1.56–1.41 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.6, 165.4, 152.8, 148.4, 145.0, 138.3, 137.5, 132.4, 129.0, 126.6, 122.4, 110.4, 106.9, 101.0, 91.9, 60.8, 56.2, 48.2, 39.0, 34.4, 27.6, 23.2, 20.8, 13.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{31}N_3O_7$534.2234; Found 534.2234.

5-acetyl-4-(2-methoxyphenyl)-3-methyl-1-phenyl-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo[4,3-g]pyrido[2,1-b][1,3]oxazocin-6(1H)-one (**3cn**): White solid (yield: 40.6 mg, 86%). M.P. = 162.3–162.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 5.8 Hz, 3H), 7.30 (t, J = 7.4 Hz, 1H), 7.21 (td, J = 8.5, 1.6 Hz, 1H), 6.88 (m, 2H), 5.51 (s, 1H), 3.92 (s, 3H), 3.89 (dd, J = 13.3, 4.6 Hz, 1H), 2.74 (d, J = 13.2 Hz, 1H), 2.56 (td, J = 13.0, 3.0 Hz, 1H), 2.20 (s, 3H), 2.00 (s, 3H), 1.96–1.87 (m, 2H), 1.81–1.68 (m, 2H), 1.52–1.37 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 166.2, 155.5, 148.4, 145.1, 138.4 130.9, 129.0, 128.9, 126.4, 125.3, 122.4, 121.0, 110.5, 110.2, 102.1, 92.0, 55.5, 39.1, 38.8, 34.4, 26.8, 23.2, 20.8, 12.7 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{27}N_3O_5$. 474.2023; Found 474.2026.

5-acetyl-3-methyl-1-phenyl-4-(thiophen-2-yl)-4,5,8,9,10,11-hexahydro-5,11a-epoxypyrazolo[4,3-g]pyrido[2,1-b][1,3]oxazocin-6(1H)-one (**3cp**): White solid (yield: 38.1 mg, 85%). M.P. = 181.6–181.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.7 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.19 (d, J = 5.0 Hz, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.90 (t, J = 14.0 Hz, 2H), 5.17 (s, 1H), 3.87 (dd, J = 13.3, 4.6 Hz, 1H), 2.76 (d, J = 13.2 Hz, 1H), 2.52 (td, J = 13.0, 3.0 Hz, 1H), 2.10 (s, 3H), 2.09 (s, 3H), 2.04–1.84 (m, 2H), 1.82–1.65 (m, 2H), 1.54–1.39 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.3, 164.9, 148.2, 144.4, 139.9, 138.2, 128.9, 127.2, 126.7, 126.5, 125.7, 122.5, 110.5, 101.3, 91.7, 43.1, 39.0, 34.4, 27.3, 23.2, 20.8, 12.8 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{23}N_3O_4S$ 450.1482; Found 450.1486.

5-acetyl-4-(4-bromophenyl)-3-methyl-1-phenyl-4,5,9,10,11,12-hexahydro-8H-5,12a-epoxyazepino[2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3db**): White solid (yield: 32.1 mg, 60%). M.P. = 212.0–212.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ7.63 (d, J = 7.5 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.40 (d, J = 8.4 Hz, 2H),7.32 (t, J = 7.4 Hz, 1H), 7.20 (d, J = 8.5 Hz, 2H), 4.77 (s, 1H), 3.86 (dd, J = 13.3, 4.6 Hz, 1H), 2.91–2.75 (m, 2H), 2.37–2.29 (m, 1H), 2.00 (s, 3H), 1.97 (s, 3H), 1.96–1.88 (m, 2H), 1.79–1.71 (m, 1H), 1.54–1.39 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 166.1, 148.0, 145.3, 138.3, 136.1, 131.5, 131.4, 129.0, 126.6, 122.5, 121.8, 115.6, 100.3, 91.4, 47.1, 40.6, 38.4, 29.5, 28.5, 27.7, 22.6, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{26}BrN3O_4$ 536.1179; Found 536.1189.

5-acetyl-4-(4-methoxyphenyl)-3-methyl-1-phenyl-4,5,9,10,11,12-hexahydro-8H-5,12a-epoxyazepino[2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3dd**): White solid (yield: 37.9 mg, 78%). M.P. = 161.0–161.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 7.5 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.5 Hz, 1H),7.22 (dd, J = 8.7, 1.9 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 4.75 (s, 1H), 3.84 (d, J = 10.6 Hz, 1H), 3.77 (s, 3H), 2.92–2.74 (m, 2H), 2.40–2.30 (m, 1H), 1.97 (s, 6H), 1.96–1.88 (m, 2H), 1.81–1.71 (m, 1H), 1.54–1.27 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 166.4, 158.9, 148.1, 145.2, 138.5, 130.7, 128.9, 126.5, 122.5, 115.4, 113.7, 100.9, 91.7, 55.2, 47.4, 40.5, 38.4, 29.5, 28.5, 27.7, 22.5, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{29}N_3O_5$ 488.2180; Found 488.2187.

5-acetyl-3-methyl-4-(naphthalen-1-yl)-1-phenyl-4,5,9,10,11,12-hexahydro-8H-5,12a-epoxyazepino[2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3de**): White solid (yield: 46.1 mg, 91%). M.P. = 183.5–183.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.78 (m, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 7.6 Hz, 2H), 7.52–7.41 (m, 5H), 7.32 (t, J = 7.4 Hz, 2H), 4.98 (s, 1H), 3.89 (d, J = 10.6 Hz, 1H), 2.98–2.77 (m, 2H), 2.40–2.30 (m, 1H), 1.99 (s, 3H), 1.98–1.94 (br, 1H), 1.95 (s, 3H), 1.94–1.91 (br, 1H), 1.81–1.71 (m, 1H), 1.54–1.27 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.5, 166.4, 148.3, 145.4, 138.5, 134.5, 133.0, 132.8, 129.0, 128.8, 128.2, 128.1, 127.6, 127.3, 126.5, 126.1, 126.1, 122.5, 115.5, 100.7, 91.8, 48.1, 40.6, 38.4, 29.6, 28.5, 27.7, 22.6, 13.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{29}N_3O_4$ 508.2230; Found 508.2239.

5-acetyl-3-methyl-4-phenyl-1-(p-tolyl)-4,5,9,10,11,12-hexahydro-8H-5,12a-epoxyazepino[2,1-b]pyrazolo [4,3-g][1,3]oxazocin-6(1H)-one (**3dg**): White solid (yield: 42.3 mg, 90%). M.P. = 191.0–191.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 6.8 Hz, 3H), 7.27–7.21 (m, 4H), 4.79 (s, 1H), 3.84 (d, J = 14.0 Hz, 1H), 2.90–2.74 (m, 2H), 2.40 (s, 3H), 2.34 (dd, J = 15.6, 10.6 Hz, 1H), 1.97 (s, 3H), 1.96 (s, 3H), 1.94–1.86 (m, 2H), 1.77–1.70 (br, 1H), 1.51–1.38 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 166.4, 147.8, 145.2, 137.0, 136.3, 136.0, 129.6, 129.5, 128.3, 127.6, 122.5, 115.3, 100.6, 91.6, 48.0, 40.5, 38.4, 29.5, 28.5, 27.6, 22.5, 21.1, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{29}N_3O_4$ 472.2230; Found 472.2236.

5-acetyl-3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-4,5,9,10,11,12-hexahydro-8H-5,12a-epoxyazepino[2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3dl**): White solid (yield: 44.8 mg, 82%). M.P. = 215.2–215.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 6.52 (s, 2H), 4.71 (s, 1H), 3.89–3.82 (br, 1H), 3.81 (s, 6H), 3.80 (s, 3H), 2.89–2.74 (m, 2H), 2.35 (dd, J = 15.6, 10.6 Hz, 1H), 2.02 (s, 3H), 1.99 (s, 3H), 1.96–1.86 (m, 2H), 1.77–1.69 (m, 1H), 1.51–1.32 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 166.3, 152.8, 148.2, 145.2, 138.4, 137.4, 132.5, 129.0, 126.6, 122.4, 115.5, 106.8, 100.6, 91.6, 60.8, 56.2, 48.3, 40.6, 38.4, 29.5, 28.5, 27.8, 22.6, 13.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{30}H_{33}N_3O_7$ 548.2391; Found 548.2404.

5-acetyl-4-(2-methoxyphenyl)-3-methyl-1-phenyl-4,5,9,10,11,12-hexahydro-8H-5,12a-epoxyazepino[2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3dn**): White solid (yield: 39.4 mg, 81%). M.P. = 190.9–191.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 6.9 Hz, 3H), 7.28 (t, J = 7.4 Hz, 1H), 7.20 (td, J = 8.7, 1.9 Hz, 1H), 6.88 (t, J = 6.1 Hz, 2H), 5.53 (s, 1H), 3.92 (s, 3H), 3.85 (dd, J = 10.6, 3.0 Hz, 1H), 2.96–2.74 (m, 2H), 2.37–2.27 (m, 1H), 2.26 (s, 3H), 2.00 (s, 3H), 1.96–1.88 (m, 2H), 1.81–1.71 (m, 1H), 1.54–1.27 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.0, 167.2, 155.4, 148.3, 145.2, 138.5, 130.9, 129.0, 128.9, 126.4, 125.5, 122.5, 121.1, 115.3, 110.5, 101.7, 91.8, 55.4, 40.4, 38.8, 38.2, 29.5, 28.5, 26.8, 22.4, 12.7 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{28}H_{29}N_3O_5$ 488.2180; Found 488.2186.

5-acetyl-4-(4-methoxyphenyl)-3-methyl-1-phenyl-4,5,8,9,10,11,12,13-octahydro-5,13a-epoxyazocino [2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3ed**): White solid (yield: 42.5 mg, 85%). M.P. = 106.5–106.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 11.6 Hz, 2H), 4.75 (s, 1H), 3.76 (s, 3H), 3.85 (dt, J = 14.4, 4.0 Hz, 1H), 2.78 (td, J = 11.9, 3.5 Hz, 1H), 2.64 (dt, J = 15.7, 4.3 Hz, 1H), 2.48 (td, J = 10.9, 4.3 Hz, 1H), 1.98 (s, 3H), 1.97 (s, 3H), 1.86–1.71 (m, 3H), 1.70–1.55 (m, 3H), 1.54–1.33 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 167.0, 158.9, 148.1, 145.1, 138.5, 130.7, 128.9, 128.8, 126.4, 122.3, 114.1, 113.7, 101.1, 91.6, 55.2, 47.7, 40.3, 31.7, 27.7, 27.0, 25.0, 23.8, 22.1, 12.9 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{29}H_{31}N_3O_5$ 502.2336; Found 502.2341.

5-acetyl-3-methyl-1-phenyl-4-(3,4,5-trimethoxyphenyl)-4,5,8,9,10,11,12,13-octahydro-5,13a-epoxya zocino[2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3el**): White solid (yield: 51.0 mg, 90%). M.P. = 223.2–223.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 7.8 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.28 (t, J = 7.4 Hz, 1H), 7.21 (d, J = 8.4 Hz, 2H), 6.50 (s, 2H), 4.71 (s, 1H), 3.81 (s, 6H), 3.80 (s, 3H), 3.64 (dt, J = 14.4, 3.9 Hz, 1H), 2.76 (td, J = 11.9, 3.5 Hz, 1H), 2.60 (dt, J = 15.7, 4.3 Hz, 1H), 2.53–2.41 (m, 1H), 2.01 (s, 3H), 1.98 (s, 3H), 1.84–1.70 (m, 3H), 1.68–1.53 (m, 3H), 1.52–1.35 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ200.7, 166.9, 152.8, 148.2, 145.1, 138.4, 137.4, 132.4, 129.0, 126.5, 122.2, 114.2, 106.8, 100.8, 91.4, 60.8, 56.2, 48.5, 40.4, 31.8, 27.8, 27.0, 25.0, 23.8, 22.1, 13.0 ppm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{35}N_3O_7$ 562.2547; Found 562.2556.

5-acetyl-4-(2-methoxyphenyl)-3-methyl-1-phenyl-4,5,8,9,10,11,12,13-octahydro-5,13a-epoxyazocino [2,1-b]pyrazolo[4,3-g][1,3]oxazocin-6(1H)-one (**3en**): White solid (yield: 25.0 mg, 50%). M.P. = 69.6–69.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.7 Hz, 3H), 7.28 (t, J = 7.4 Hz, 1H), 7.21 (td, J = 8.4, 1.6 Hz, 1H), 6.92–6.85 (m, 2H), 5.51 (s, 1H), 3.93 (s, 3H), 3.67 (dt, J = 14.4, 4.0 Hz, 1H), 2.80 (td, J = 11.9, 3.5 Hz, 1H), 2.65 (dq, J = 15.7, 3.6 Hz,

1H), 2.44 (td, *J* = 10.9, 4.3 Hz, 1H), 2.24 (s, 3H), 1.99 (s, 3H), 1.86–1.69 (m, 3H), 1.64–1.55 (m, 3H), 1.54–1.39 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 167.9, 155.5, 148.3, 145.1, 138.6, 131.0, 128.9, 128.9, 126.3, 125.3, 122.3, 121.1, 114.0, 110.5, 101.9, 91.5, 55.4, 40.1, 39.3, 32.0, 26.9, 26.8, 25.3, 23.9, 22.1, 12.7 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{21}H_{31}N_3O_5$ 502.2336; Found 502.2338.

7-benzoyl-12-benzyl-2,3,7,12-tetrahydro-1H-6,13a-epoxypyrrolo[2′,1′:2,3][1,3]oxazocino[8,7-b]indol-5(6H)-one (**3bq**): White solid (yield: 42.2 mg, 91%). M.P. = 114.5–114.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.29 (m, 6H), 7.22 (t, *J* = 3.56 Hz, 2H), 7.14 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 7.01 (td, *J* = 7.7, 1.2 Hz, 1H), 6.89 (td, *J* = 7.7, 1.2Hz, 1H), 6.47 (d, *J* = 7.8 Hz, 2H), 5.37 (s, 1H), 5.03 (d, *J* = 15.1 Hz, 1H), 4.63 (d, *J* = 15.4 Hz, 1H), 4.59 (s, 1H), 3.83–3.75 (m, 1H), 3.22–3.15 (m, 1H), 2.12–2.03 (m, 1H), 1.89–1.80 (m, 2H), 1.26–1.19 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 173.5, 173.5, 142.5, 136.3, 135.5, 133.0, 128.9, 128.9, 128.3, 127.9, 127.6, 127.4, 126.3, 125.4, 123.0, 108.5, 108.4, 81.4, 59.6, 56.6, 44.3, 42.6, 26.3, 25.8 ppm; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ Calcd for $C_{29}H_{24}N_2O_4$ 465.1809; Found 465.1761.

4. Conclusions

Conclusively, under the catalysis of $Rh_2(OAc)_4$ and binapbisphosphine ligand (±)-**L3** in DCE at 80 °C, the cascade cyclization of diazoimides with alkylidenepyrazolones underwent diastereoselectively (dr > 20:1), affording pyrazole-fused oxa-bridged oxazocines in reasonable chemical yields. Moreover, the design and exploration of other novel cyclic carbonyl-ylide-based cyloadditions is ongoing in our organic lab, and will be reported in due course.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules28207021/s1, NMR spectral copies of products **3**–**7**. X-ray crystal data of products **3aa** and **4**.

Author Contributions: Funding acquisition, project administration, supervision, writing—original draft preparation, H.-W.Z.; investigation, methodology, formal analysis, data curation, writing—review and editing, K.W.; investigation, methodology, Y.Z., L.-Y.C., X.-Q.S., C.W., J.-R.Z. and Y.-F.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Beijing Municipal Commission of Education (No. JC015001200902), Beijing Municipal Natural Science Foundation (No. 7102010, No. 2122008, No. 2172003, No. 2222002), Basic Research Foundation of Beijing University of Technology (X4015001201101), Funding Project for Academic Human Resources Development in Institutions of Higher Learning Under the Jurisdiction of Beijing Municipality (No. PHR201008025), Doctoral Scientific Research Start-up Foundation of Beijing University of Technology (No. 52015001200701) for financial supports.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

Sample Availability: Samples of the compounds are available from the authors.

References

1. Parrino, B.; Cascioferro, S.; Carbone, D.; Cirrincione, G.; Diana, P. Eight-membered heterocycles with two heteroatoms in a 1,5-relationship of interest in medicinal chemistry. *Adv. Heterocycl. Chem.* **2020**, *132*, 135–239.
2. Parrino, B.; Cascioferro, S.; Carbone, D.; Pecoraro, C.; Cirrincione, G.; Diana, P. Eight-membered heterocycles with two heteroatoms in a 1,3-relationship of interest in medicinal chemistry. *Adv. Heterocycl. Chem.* **2022**, *136*, 1–57.
3. Bera, M.; Roy, S. Silver(I)-catalyzed dual activation of propargylic alcohol and aziridine/azetidine: Triggering ring-opening and endo-selective ring-closing in a cascade. *J. Org. Chem.* **2009**, *74*, 8814–8817. [CrossRef]

4. Ghosh, A.; Hegde, R.V.; Rode, H.B.; Ambre, R.; Mane, M.V.; Patil, S.A.; Sridhar, B.; Dateer, R.B. Catalyst- and additive-free approach to constructing benzo-oxazine, benzo-oxazepine, and benzo-oxazocine: O atom transfer and C horizontal lineo, C-N, and C-O bond formation at room temperature. *Org. Lett.* **2021**, *23*, 8189–8193. [CrossRef]
5. Mondal, S.; Paira, R.; Maity, A.; Naskar, S.; Sahu, K.B.; Hazra, A.; Saha, P.; Banerjee, S.; Mondal, N.B. Basic alumina supported tandem synthesis of bridged polycyclic quinolino/isoquinolinooxazocines under microwave irradiation. *Tetrahedron Lett.* **2011**, *52*, 4697–4700. [CrossRef]
6. Neogi, A.; Majhi, T.P.; Mukhopadhyay, R.; Chattopadhyay, P. Palladium-mediated intramolecular aryl amination on furanose derivatives: An expedient approach to the synthesis of chiral benzoxazocine derivatives and tricyclic nucleosides. *J. Org. Chem.* **2006**, *71*, 3291–3294. [CrossRef] [PubMed]
7. Niu, S.S.; Cheng, Y. Construction of novel bridged aromatic ring-fused oxazocine frameworks via an N-heterocyclic Carbene-catalyzed azabenzoin reaction and radical-initiated cascade cyclization. *Org. Chem. Front.* **2021**, *8*, 4192–4201. [CrossRef]
8. Pramthaisong, C.; Worayuthakarn, R.; Pharikronburee, V.; Duangthongyou, T.; Rattanakam, R.; Ruchirawat, S.; Thasana, N. Base-mediated cascade cyclization: Stereoselective synthesis of benzooxazocinone. *Org. Lett.* **2018**, *20*, 4015–4019. [CrossRef]
9. Goutham, K.; Ashok Kumar, D.; Suresh, S.; Sridhar, B.; Narender, R.; Karunakar, G.V. Gold-catalyzed intramolecular cyclization of N-propargylic beta-enaminones for the synthesis of 1,4-oxazepine derivatives. *J. Org. Chem.* **2015**, *80*, 11162–11168. [CrossRef] [PubMed]
10. Lam, H.; Qureshi, Z.; Wegmann, M.; Lautens, M. Transition-metal-free [4+3]-cycloaddition of *ortho*-quinonemethides and isomünchnones: Catalytic and diastereoselective assembly of oxa-bridged oxazocine scaffolds. *Angew. Chem.* **2018**, *130*, 16417–16421. [CrossRef]
11. Li, Q.; Pan, R.; Wang, M.; Yao, H.; Lin, A. Ligand-controlled, palladium-catalyzed asymmetric [4+4] and [2+4] cycloadditions. *Org. Lett.* **2021**, *23*, 2292–2297. [CrossRef] [PubMed]
12. Ramachary, D.B.; Narayana, V.V.; Prasad, M.S.; Ramakumar, K. High-yielding synthesis of nefopam analogues (functionalized-benzoxazocines) by sequential one-pot cascade operations. *Org. Biomol. Chem.* **2009**, *7*, 3372–3378. [CrossRef] [PubMed]
13. Xie, H.; Chen, L.; Han, Z.; Yang, Z.; Sun, J.; Huang, H. Pd-catalyzed ligand-directed divergent cycloaddition of cyclic 1-azadienes with oxo-1,4-dipoles. *Org. Lett.* **2023**, *25*, 5011–5016. [CrossRef] [PubMed]
14. Xu, C.; Wang, K.; Li, D.; Lin, L.; Feng, X. Asymmetric synthesis of oxa-bridged oxazocines through a catalytic Rh(II)/Zn(II) relay [4 + 3] cycloaddition reaction. *Angew. Chem.* **2019**, *58*, 18438–18442. [CrossRef] [PubMed]
15. Doxsee, K.M. *Eight-membered rings with two heteroatoms 1,3. Comprehensive Heterocyclic Chemistry II*; Elsevier: Amsterdam, The Netherlands, 1996; pp. 495–525.
16. Ford, A.; Miel, H.; Ring, A.; Slattery, C.N.; Maguire, A.R.; McKervey, M.A. Modern organic synthesis with alpha-diazocarbonyl compounds. *Chem. Rev.* **2015**, *115*, 9981–10080. [CrossRef]
17. Padwa, A. Domino reactions of Rhodium(II) carbenoids for alkaloid synthesis. *Chem. Soc. Rev.* **2009**, *38*, 3072–3081. [CrossRef]
18. Anderson, R.J.; Raolji, G.B.; Kanazawa, A.; Greene, A.E. A novel, expeditious synthesis of racemic camptothecin. *Org. Lett.* **2005**, *7*, 2989–2991. [CrossRef]
19. Padwa, A. Cycloaddition chemistry of carbonyl ylides for alkaloid synthesis. *Russ. Chem. Bull.* **2017**, *65*, 2183–2194. [CrossRef]
20. Padwa, A.; Austin, D.J.; Price, A.T.; David Weingarten, M. Studies on the intramolecularcycloaddition reaction of isomünchnones derived from n-alkenyl substituted diazoimides. *Tetrahedron* **1996**, *52*, 3247–3260. [CrossRef]
21. Padwa, A.; Lynch, S.M.; Mejia-Oneto, J.M.; Zhang, H. Cycloaddition chemistry of 2-vinyl-substituted indoles and related heteroaromatic systems. *J. Org. Chem.* **2005**, *70*, 2206–2218. [CrossRef]
22. Padwa, A.; Prein, M. Acyclic stereocontrol in [3 + 2]-cycloadditions of amino acid-derived isomünchnone dipoles. *Tetrahedron* **1998**, *54*, 6957–6976. [CrossRef]
23. Straub, C.S.; Padwa, A. Synthesis of the angiotensin converting enzyme inhibitor (−)-a58365a via an isomunchnonecycloaddition reaction. *Org. Lett.* **1999**, *1*, 83–85. [CrossRef] [PubMed]
24. Mills, M.C.; Wright, D. Carbonyl ylides. In *Chemistry of Heterocyclic Compounds*; Springer: Berlin/Heidelberg, Germany, 2003; pp. 253–314.
25. Padwa, A.; Weingarten, M.D. Cascade processes of metallocarbenoids. *Chem. Rev.* **1996**, *96*, 223–270. [CrossRef] [PubMed]
26. Doyle, M.P.; Pieters, R.J.; Taunton, J.; Pho, H.Q.; Padwa, A.; Hertzog, D.L.; Precedo, L. Synthesis of nitrogen-containing polycycles via Rhodium(II)-induced cyclization-cycloaddition and insertion reactions of n-(diazoacetoacetyl)amides. Conformational control of reaction selectivity. *J. Org. Chem.* **2002**, *56*, 820–829. [CrossRef]
27. Gonzalez, R.; Knight, B.W.; Wudl, F.; Semones, M.A.; Padwa, A. The reversible cycloaddition of isomunchnones to C_{60}. *J. Org. Chem.* **2002**, *59*, 7949–7951. [CrossRef]
28. Padwa, A.; Hertzog, D.L.; Nadler, W.R.; Osterhout, M.H.; Price, A.T. Studies on the intramolecularcycloaddition reaction of mesoionics derived from the Rhodium(II)-catalyzed cyclization of diazoimides. *J. Org. Chem.* **2002**, *59*, 1418–1427. [CrossRef]
29. Prein, M.; Manley, P.J.; Padwa, A. Site selectivity in the Rhodium(II)-catalyzed reaction of α-diazoimides. Ligand and substituent effects. *Tetrahedron* **1997**, *53*, 7777–7794. [CrossRef]
30. Sheehan, S.M.; Padwa, A. New synthetic route to 2-pyridones and its application toward the synthesis of (+/−)-ipalbidine. *J. Org. Chem.* **1997**, *62*, 438–439. [CrossRef] [PubMed]
31. Hodgson, D.M.; Labande, A.H.; Muthusamy, S. Cycloadditions of carbonyl ylides derived from diazocarbonyl compounds. *Org. React.* **2013**, *80*, 133–496.

32. Mehta, G.; Muthusamy, S. Tandem cyclization–cycloaddition reactions of Rhodium generated carbenoids from α-Diazo carbonyl compounds. *Tetrahedron* **2002**, *58*, 9477–9504. [CrossRef]
33. Padwa, A.; Hornbuckle, S.F. Ylide formation from the reaction of carbenes and carbenoids with heteroatom lone pairs. *Chem. Rev.* **2002**, *91*, 263–309. [CrossRef]
34. Marino, J.P.; Osterhout, M.H.; Price, A.T.; Semones, M.A.; Padwa, A. Synthesis of tricyclic nitrogen compounds via a tandem cyclization-cycloaddition-cationic cyclization sequence. *J. Org. Chem.* **2002**, *59*, 5518–5520. [CrossRef]
35. Miah, S.; Slawin, A.M.Z.; Moody, C.J.; Sheehan, S.M.; Marino, J.P.; Semones, M.A.; Padwa, A.; Richards, I.C. Ligand effects in the Rhodium(II) catalysed reactions of diazoamides and diazoimides. *Tetrahedron* **1996**, *52*, 2489–2514. [CrossRef]
36. De, N.; Ko, D.; Yoo, E.J. Rhodium(II)-catalyzed 1,3- and 1,5-dipolar cycloaddition. *Rhodium Catal. Org. Synth.* **2019**, 471–486. [CrossRef]
37. Suga, H.; Itoh, K. Recent advances in catalytic asymmetric 1,3-dipolar cycloadditions of azomethine imines, nitrile oxides, diazoalkanes, and carbonyl ylides. *Methods Appl. Cycloaddit. React. Org. Synth.* **2014**, 175–204. [CrossRef]
38. Padwa, A.; Hertzog, D.L.; Chinn, R.L. Synthesis of aza substituted polycycles via Rhodium (II) carboxylate induced cyclization of diazoimides. *Tetrahedron Lett.* **1989**, *30*, 4077–4080. [CrossRef]
39. Wang, J.; Liu, X.-J.; Chen, D.-Z.; Liu, J.-B. Mechanistic insights into catalyst-dependent divergent cycloaddition reactions via discrimination between diazo compounds. *Org. Chem. Front.* **2023**, *10*, 1606–1616. [CrossRef]
40. Wang, K.; Xu, C.; Hu, X.; Zhou, Y.; Lin, L.; Feng, X. Catalytic asymmetric [3+2] cycloaddition of isomunchnones with methyleneindolinones. *Chem. Commun.* **2021**, *57*, 8917–8920. [CrossRef]
41. Bania, N.; Barman, D.; Pan, S.C. Organocatalytic asymmetric inverse-electron-demand diels-alder reaction between alkylidenepyrazolones and allyl ketones: Access to tetrahydropyrano[2,3-c]pyrazoles. *J. Org. Chem.* **2023**, *88*, 9584–9593. [CrossRef]
42. Guo, J.M.; Fan, X.Z.; Wu, H.H.; Tang, Z.; Bi, X.F.; Zhang, H.; Cai, L.Y.; Zhao, H.W.; Zhong, Q.D. Asymmetric synthesis of spiropyrazolones via chiral Pd(0)/ligand complex-catalyzed formal [4+2] cycloaddition of vinyl benzoxazinanones with alkylidenepyrazolones. *J. Org. Chem.* **2021**, *86*, 1712–1720. [CrossRef] [PubMed]
43. Meninno, S.; Roselli, A.; Capobianco, A.; Overgaard, J.; Lattanzi, A. Diastereodivergent and enantioselective access to spiroepoxides via organocatalyticepoxidation of unsaturated pyrazolones. *Org. Lett.* **2017**, *19*, 5030–5033. [CrossRef]
44. Xu, H.; Hong, R.; Weng, M.Y.; Huang, R.L.; Wang, G.W.; Zhang, Z. Regiodivergent synthesis of 4,5′- and 4,4′-imidazolinyl spiropyrazolones from 4-alkylidene pyrazolones and amidines. *Org. Lett.* **2021**, *23*, 5305–5310. [CrossRef]
45. CCDC 2260380 (**3aa**) and CCDC 2260381 (**4**) Contain the Supplementary Crystallographic Data for this Paper. These Data can be Obtained Free of Charge from The Cambridge Crystallographic Data Center. X-ray Single Crystal Structures of **3aa** and **4** were Shown with Thermal Ellipsoils Shown at the 50% Probability Level. Available online: http://www.ccdc.camac.uk/data_request/cif (accessed on 5 March 2023).
46. Padwa, A.; Hornbuckle, S.F.; Fryxell, G.E.; Stull, P.D. Reactivity patterns in the rhodium carbenoid induced tandem cyclization-cycloaddition reaction. *J. Org. Chem.* **1989**, *54*, 817–824. [CrossRef]
47. Padwa, A.; Hertzog, D.L. Bimolecular cycloaddition reactions of isomünchnones derived from the rhodium(II) catalyzed cyclization of diazopyrrolidinones. *Tetrahedron* **1993**, *49*, 2589–2600. [CrossRef]
48. Sheibani, H.; Babaie, M. Three-component reaction to form 1,4-dihydropyrano[2,3-c]pyrazol-5-yl cyanides. *Synth. Commun.* **2009**, *40*, 257–265. [CrossRef]
49. Khairnar, P.V.; Su, Y.H.; Edukondalu, A.; Lin, W. Enantioselective synthesis of spiropyrazolone-fused cyclopenta[c]chromen-4-ones bearing five contiguous stereocenters via [3+2] cycloaddition. *J. Org. Chem.* **2021**, *86*, 12326–12335. [CrossRef]
50. Zhao, C.; Shi, K.; He, G.; Gu, Q.; Ru, Z.; Yang, L.; Zhong, G. Nhc-catalyzed asymmetric formal [4+2] annulation to construct spirocyclohexanepyrazolone skeletons. *Org. Lett.* **2019**, *21*, 7943–7947. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.