OL | Organic Letters

pubs.acs.org/OrgLett Letter

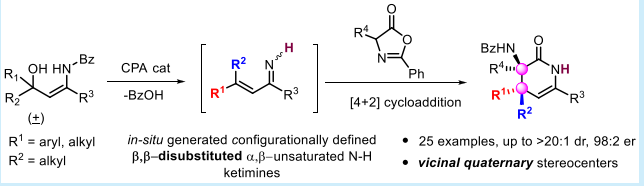
Asymmetric Aza-Diels–Alder Reactions of in Situ Generated β,β-Disubstituted α,β-Unsaturated N–H Ketimines Catalyzed by Chiral Phosphoric Acids

Shunlong He, Huanchao Gu, Yu-Peng He,* and Xiaoyu Yang*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01994 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A novel asymmetric synthesis of dihydropyridinones with vicinal quaternary stereocenters has been realized by asymmetric aza-Diels–Alder reactions of 3-amido allylic alcohols with oxazolones enabled by chiral phosphoric acid catalysis. A series of aryl/alkyl- and alkyl/alkyl-disubstituted 3-amido allylic tertiary alcohols and 4-substituted oxazolones could be well tolerated in these reactions, producing dihydropyridinones with excellent diastereoselectivities and high enantioselectivities. Mechanistic study and control experiments were performed to shed light on the reaction mechanism, in which a configurationally defined β,β-disubstituted α,β-unsaturated N–H ketimine was proposed as the key intermediate.



Dihydropyridinones are a type of privileged six-membered azacycles, which are widely present in a series of biologically active small molecules and natural products.[1] Among various synthetic methods for preparation of these heterocycles, the inverse-electron-demand aza-Diels–Alder (ADA) reaction[2] is one of the most efficient methods, which was pioneered by Boger and co-workers.[3] The asymmetric catalytic versions[4] of these reactions have also drawn considerable research interest due to the significance of chiral dihydropyridinone scaffolds, and numerous of elegant enantioselective methods have been developed in the past two decades. In general, an enolate-type (or enolate analog) intermediate is generated under diverse catalytic systems, which undergoes the enantioselective aza-Diels–Alder reactions with α,β-unsaturated imines to generate the chiral dihydropyridinone products.[5] Since the landmark work of using chiral N-heterocyclic carbene (NHC) catalysts in the asymmetric ADA reactions between enals and α,β-unsaturated imines by Bode and co-workers,[6] asymmetric NHC catalysis has become a versatile approach for the synthesis of enantioenriched dihydropyridinones, using ketenes,[7] α-chloroaldehyde,[8] and alkylacetic ester[9] as enolate precursors by Ye and Chi group, respectively. The Smith group disclosed enantioselective synthesis of dihydropyridinones through asymmetric ADA reactions between α,β-unsaturated imines and arylacetic acids[10] and *N*-acyl imidazoles[11] via chiral isothiourea catalysis. The Gong group reported the asymmetric three-component ADA reaction between enals, anilines, and oxazolones under chiral Brønsted acid catalysis[12] (Figure 1a, top). On the other hand, asymmetric ADA reactions have also been well employed in the asymmetric synthesis of tetrahydropyridine derivatives via cycloadditions between

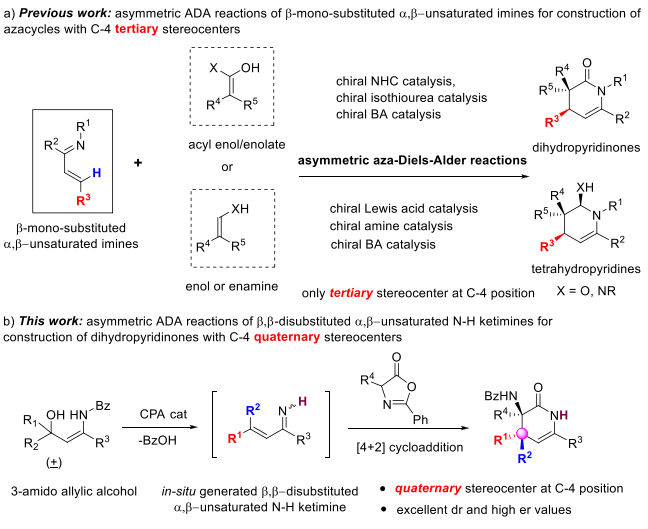


Figure 1. Asymmetric aza-Diels–Alder reactions of α,β-unsaturated imines.

enols/enamines and α,β-unsaturated imines, which could be enabled by chiral Lewis acid catalysis,[13] chiral amine catalysis,[14] and chiral Brønsted acid catalysis (Figure 1a, bottom).[15]

Received: June 15, 2020

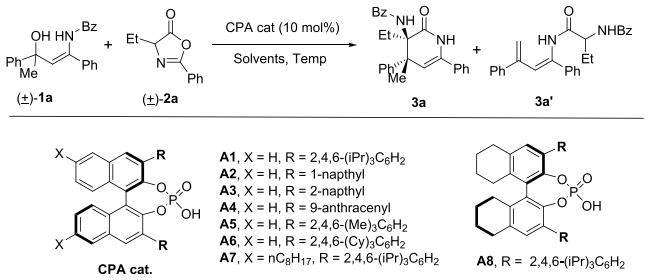
https://dx.doi.org/10.1021/acs.orglett.0c01994
Org. Lett. XXXX, XXX, XXX–XXX

Despite the fact that a series of different asymmetric catalytic methods have been developed for asymmetric synthesis of dihydropyridinones and tetrahydropyridines via enantioselective ADA reactions, the other coupling partner for cycloaddition in these reactions was limited to α,β-unsaturated imines possessing a mono-β-substitution, thus leading to the generation of azacyles with only a tertiary stereocenter at the C-4 position.[5f,g] To the best of our knowledge, no example of β,β-disubstituted α,β-unsaturated imine precursors has been utilized in asymmetric ADA reactions, probably due to their relatively low reactivities and challenges in stereoselectivities control. With our continuous interest in developing novel asymmetric reactions of amido allylic alcohols,[16] herein we report a novel asymmetric synthesis of dihydropyridinones with vicinal quaternary stereocenters via enantioselective aza-Diels–Alder reactions between 3-amido allylic alcohols and oxazolones[17] enabled by chiral phosphoric acid (CPA) catalysis,[18] in which an *in situ* generated β,β-disubstituted α,β-unsaturated N–H ketimine[19] was proposed as the key intermediate (Figure 1b).

We commenced our study by choosing racemic 3-amido allylic alcohol **1a** and oxazolone **2a** as model substrates under CPA catalysis (Table 1). The initial attempt between these two substrates (1:1 mol ratio) under the catalysis of TRIP catalyst (cat **A1**, 10 mol %) in toluene in the presence of acid-wash molecular sieves (AW-300 MS) at 25 °C successfully produced the dihydropyridinone **3a** in 30% yield with >20:1 diastereoselectivity and 91:9 enantiomeric ratio (er) (entry 1). Interestingly, the *N*-1 benzoyl group of the product was removed under these conditions. Next, a series of solvents were first examined (entries 2–4), indicating CCl_4 was the optimal one, in which an improved er was afforded (entry 4). Subsequently, a range of BINOL-derived CPA catalysts were screened; however, unfortunately, none of them could provide improved results (entries 5–9). Interestingly, using C_8-TRIP (cat **A7**) as catalyst led to an improved yield with retained er (entry 10), while switching the chiral scaffold to H8-BINOL type did not provide better results (entry 11). Due to the vulnerability of **1a** under these conditions, increasing the amount of **1a** to 1.5 equiv provided significantly improved yield (entry 12). Finally, decreasing the reaction temperature to 18 °C generated the dihydropyridinones **3a** in 61% yield with >20:1 dr and 95:5 er (entry 13; see Table S1 in the Supporting Information (SI) for more optimization conditions).[20] It is worth mentioning that the oxazolone ring-opening addition product **3a′** was isolated as the major byproduct in 27% yield with 55.5:44.5 er under these optimal conditions.

With the optimal conditions in hand, we sought to explore the scope of this reaction (Scheme 1). A series of aryl groups at the 1-position of 3-amido allylic alcohols **1** were first examined, and we found that various *para*- and *meta*-substituted phenyl groups could be well tolerated under the optimal conditions

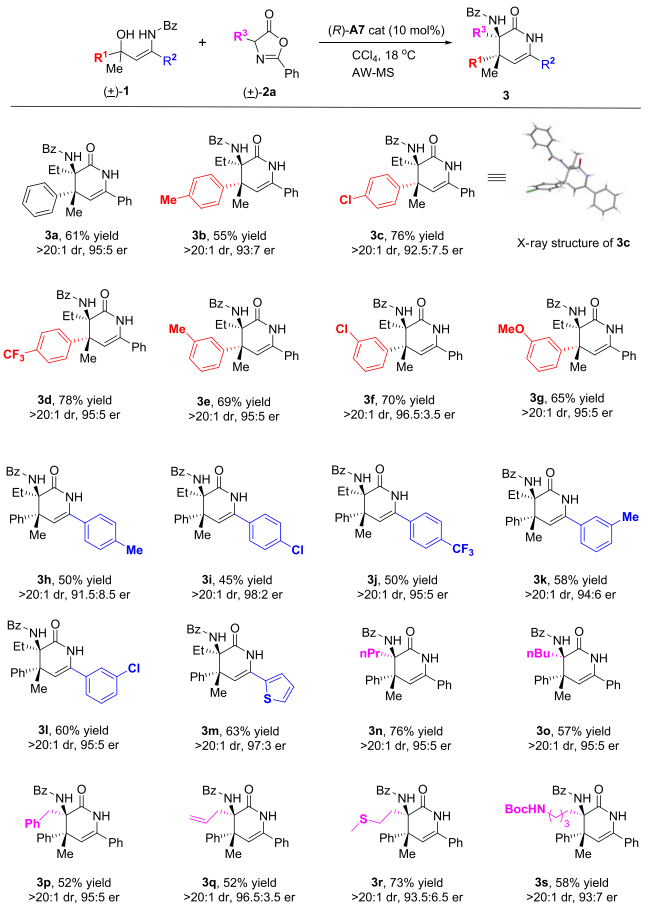
Table 1. Optimization of Reaction Conditions[a]



entry[a]	cat.	solvents	yield[b]	dr[c]	er[d]
1	**A1**	toluene	30	>20:1	91:9
2	**A1**	DCM	11	>20:1	85:15
3	**A1**	$CHCl_3$	23	>20:1	89.5:10.5
4	**A1**	CCl_4	37	>20:1	93.5:6.5
5	**A2**	CCl_4	16	>20:1	78:22
6	**A3**	CCl_4	24	>20:1	62.5:37.5
7	**A4**	CCl_4	13	>20:1	93.5:6.5
8	**A5**	CCl_4	24	>20:1	91.5:8.5
9	**A6**	CCl_4	28	>20:1	91:9
10	**A7**	CCl_4	44	>20:1	93:7
11	**A8**	CCl_4	34	>20:1	92.5:7.5
12[e]	**A7**	CCl_4	56	>20:1	93.5:6.5
13[e,f]	**A7**	CCl_4	61	>20:1	95:5

[a]Reactions were performed with **1a** (0.1 mmol), **2a** (0.1 mmol), CPA catalyst (0.01 mmol), solvents (1 mL), AW-300 MS (10 mg) at 25 °C. [b]Isolated yield. [c]Dr value was determined by NMR analysis. [d]Er value was determined by HPLC analysis on a chiral stationary phase. [e]**1a** (0.15 mmol) was used. [f]At 18 °C.

Scheme 1. Scope for Enantioselective Synthesis of Dihydropyridinones with Vicinal Chiral Quaternary Stereocenters[a]



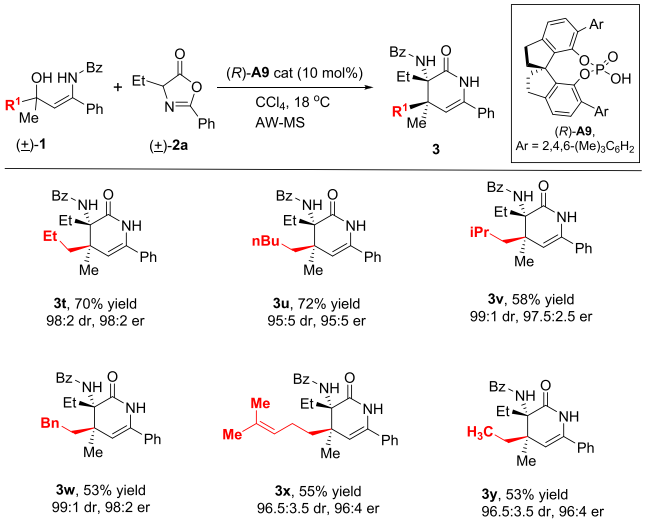
[a]Reactions were performed with **1** (0.15 mmol), **2** (0.1 mmol), (*R*)-**A7** cat (0.01 mmol), CCl_4 (1 mL), AW-300 MS (10 mg) at 18 °C for 40 h. Yields were isolated yield. Dr values were determined by NMR analysis. Er values were determined by HPLC analysis on a chiral stationary phase.

https://dx.doi.org/10.1021/acs.orglett.0c01994
Org. Lett. XXXX, XXX, XXX–XXX

(**3b**−**3g**), generating the dihydropyridinone products with excellent diastereoselectivities and high enantioselectivities. The absolute configurations of the dihydropyridinone products were confirmed by analogy to product **3c**, whose structure was unambiguously assigned by X-ray crystallography (CCDC 1993830).[20] Next, we investigated the scope of the substitutions at the 3-position of allylic alcohols. Encouragingly, a variety of substituted phenyl groups were amenable with the standard conditions (**3h**−**3l**), as well as a thienyl substituent (**3m**). Finally, the scope of the 4-subsitutions of oxazolone **2** was also explored, and a range of alkyl groups were well compatible with the optimal conditions (**3n**−**3o**), as well as the benzyl (**3p**) and allyl groups (**3q**). In addition, the functional group-containing substituents were also well tolerated, producing the products with high stereoselectivities (**3r** and **3s**).

To further extend the scope of these reactions, *n*Pr/Me-disubstituted 3-amido allylic alcohol **1t** was examined under the optimal conditions, however, which provided the dihydropyridinone product with poor enantioselectivity.[20] Encouragingly, after brief optimizations of the CPA catalysts (see Table S2 in SI), the 2,4,6-trimethylphenyl substituted SPINOL-derived phosphoric acid (*R*)-**A9** was determined to be the optimal catalyst for this reaction, which generated the product in 70% yield with 98:2 dr and 98:2 er (Scheme 2, **3t**).

Scheme 2. Scope for Enantioselective Synthesis of Dihydropyridinones from Dialkyl-Substituted 3-Amido Allylic Alcohols[a]

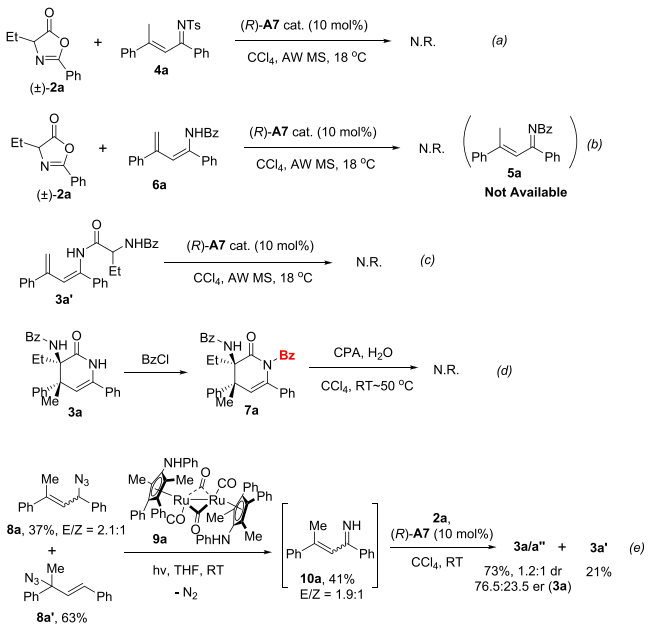


[a]Reactions were performed with **1** (0.15 mmol), **2a** (0.1 mmol), (*R*)-**A9** cat (0.01 mmol), CCl_4 (1 mL), AW-300 MS (10 mg) at 18 °C for 40 h. Yields were isolated yields. Dr and er values were determined by HPLC analysis on a chiral stationary phase.

Subsequently, a series of alkyl groups were examined at the 1-position of the allylic alcohols, which provided the dihydropyridinones with high diastereo- and enantioselectivities (**3u** and **3v**), including the aryl- and olefine-containing substituents (**3w** and **3x**). It is worth mentioning that even the Et/Me-disubstituted 3-amido allylic alcohol could afford the product with excellent stereoselectivity under the standard conditions without exception (**3y**).

To shed light on the reaction mechanism and demonstrate the uniqueness of these reactions, some control experiments were performed (Scheme 3). Treatment of oxazolone **2a** with the *β*,*β*-disubstituted *α*,*β*-unsaturated *N*-tosyl ketimine **4a**[9] did

Scheme 3. Control Experiments and Mechanistic Studies



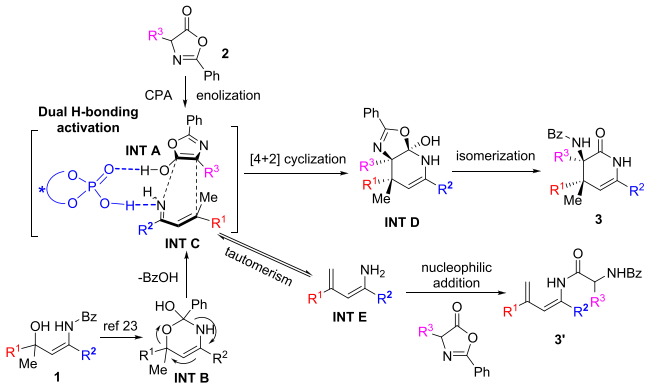
not afford any desired dihydropyridinone product under the standard conditions (Scheme 3a). In an attempt to prepare the *β*,*β*-disubstituted *α*,*β*-unsaturated *N*-benzoyl imine **5a** via condensation[9] between the corresponding enone and $BzNH_2$, only the dienamide product **6a** was obtained. Theoretically, this dienamide could still undergo isomerization to give the *α*,*β*-unsaturated imine **5a** under CPA catalysis conditions; however, no dihydropyridinone product was detected in the reaction between dienamide **6a** and oxazolone **2a** under the standard conditions, as well as no oxazolone ring-opening addition product (Scheme 3b). Treatment of the oxazolone ring-opening addition product **3a**′ with the standard conditions could not provide any dihydropyridinone product, which indicated **3a**′ was probably not an intermediate in these cycloaddition reactions (Scheme 3c). The absence of the *N*-1 Bz group in the products is a key feature of these reactions, which is also very important to understand the reaction mechanism. Selective benzoylation of the dihydropyridinone product **3a** gave the *N*-1 benzoylated product **7a**, whose structure was confirmed by 2D NMR analysis. Treatment of **7a** with CPA catalyst **A7** and H_2O did not give any debenzoylation product, even at higher reaction temperature, which suggested that **7a** was also not an intermediate of these reactions[21] (Scheme 3d). All these results clearly suggested that the *α*,*β*-unsaturated N-Bz ketimine **5a** is probably not the intermediate in these reactions. Accordingly, we envisioned that the relatively rare *α*,*β*-unsaturated N−H ketimine may be the key intermediate of these cycloaddition reactions. To prove this hypothesis, irradiation of the mixture of *α*- and *γ*-allyl azides[22] (**8a** and **8a**′) by ruthenium catalysis (**9a**) under fluorescent light in THF led to the formation of *α*,*β*-unsaturated N−H ketimine (**10a**) in 41% conversion, which existed as an *E*/*Z* mixture.[23] After removal of the solvent, the obtained crude mixture was directly subjected into the standard reaction conditions with oxazolone **2a**, which finally provided the desired dihydropyridinone **3a** in 39% yield with

https://dx.doi.org/10.1021/acs.orglett.0c01994
Org. Lett. XXXX, XXX, XXX−XXX

76.5:23.5 er, with the diastereomer **3a′′** in 34% yield and oxazolone ring-opening product **3a′** in 21% yield (Scheme 3e).[20]

Based on these results and previous reports, a plausible reaction mechanism was proposed (Scheme 4). First, the

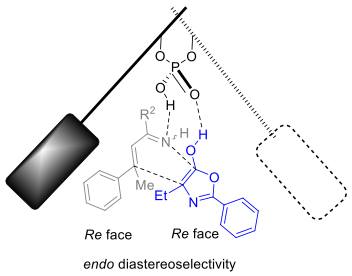
Scheme 4. Plausible Reaction Mechanism



oxazolone **2** was activated by CPA catalyst to generate its active enol form **INT A**;[12,17k,o] at the same time, the CPA also mediated the addition of the hydroxyl group to amide group in **1** to generate the orthoester **INTB**,[24] which then underwent the rearrangement to give the configurationally defined *α,β*-unsaturated N−H ketimine **INT C**. Subsequently, dual hydrogen bonding activation of the enol form of oxazolone (**INT A**) and *α,β*-unsaturated N−H ketimine **INT C** led to the facile [4 + 2] cycloaddition,[25] generating the bicyclic intermediate **INT D**, which then went through the isomerization process to give the dihydropyridinone product **3**. On the other hand, the *α,β*-unsaturated N−H ketimine **INT C** could also undergo the imine−enamine tautomerism to generate the primary dienamide **INT E**, which would attack the oxazolone to give the ring-opening addition byproduct **3′**.

To account for the observed stereoselectivities, a possible stereochemical model was depicted (Scheme 5). Through the

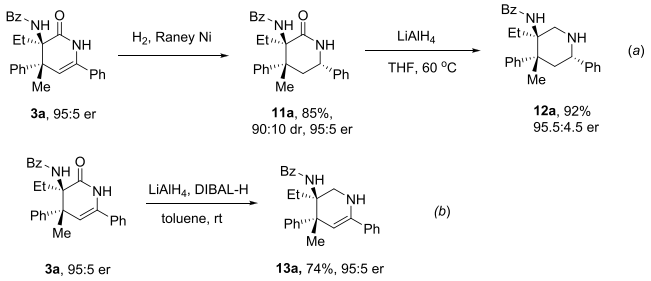
Scheme 5. Possible Stereochemical Model



bifunctional activation of the *α,β*-unsaturated N−H ketimine intermediate and the enol form of oxazolone via dual hydrogen-bonding activation with the CPA catalyst, the *Re* face of the enol form of oxazolone attacks the *Re* face of *α,β*-unsaturated N−H ketimine in an *endo*-type fashion to generate the (3*R*,4*R*)-dihydropyridinone products.

To demonstrate the applicability of these reactions, the derivatizations of the chiral products were studied (Scheme 6). Catalytic hydrogenation of dihydropyridinone **3a** using Raney Ni as the catalyst generated the pyridinone **11a** in 85% yield with 90:10 dr, whose relative configuration was assigned by

Scheme 6. Derivatizations of the Chiral Products



NOE analysis.[20] Further reduction of **11a** with $LiAlH_4$ afforded the piperidine **12a** in 92% yield, without erosion of the optical purity (Scheme 6a). Direct subjection of dihydropyridinone **3a** into the reduction with the mixture of DIBAL-H and $LiAlH_4$[26] produced the tetrahydropyridine **13a** in 74% yield with retained ee (Scheme 6b).

In conclusion, we have disclosed a novel asymmetric synthesis of dihydropyridinones bearing vicinal chiral quaternary stereocenters via enantioselective aza-Diels−Alder reaction between 3-amido allylic alcohols and oxazolones enabled by chiral phosphoric acid catalysis. A wide array of substituents at the 1- and 3-position of 3-amido allylic tertiary alcohols and 4-position of oxazolones could be well tolerated, generating dihydropyridinones with excellent diastereoselectivities and high enantioselectivities, especially highlighting the compatibility of the 1,1-dialkyl substituted 3-amido allylic alcohols. Control experiments were performed to elucidate the mechanism of these reactions, in which a configurationally defined *β,β*-disubstituted *α,β*-unsaturated N−H ketimine was proposed as the key intermediates for these asymmetric [4 + 2] cycloaddition reactions. Further application of this protocol for *in situ* generation of reactive *α,β*-unsaturated N−H ketimine intermediates in CPA catalyzed asymmetric reactions was under investigation in our lab, especially for the asymmetric construction of chiral quaternary stereocenters.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01994.

Full experiment procedures, spectroscopic characterizations, NMR and HPLC spectra (PDF)

Accession Codes

CCDC 1993830 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.

■ AUTHOR INFORMATION

Corresponding Authors

Yu-Peng He − *College of Chemistry, Chemical Engineering and Environmental Engineering, Liaoning Shihua University, Fushun 113001, China*; Email: yupeng.he@lnpu.edu.cn

Xiaoyu Yang − *School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China*; orcid.org/0000-0002-0756-0671; Email: yangxy1@shanghaitech.edu.cn

https://dx.doi.org/10.1021/acs.orglett.0c01994
Org. Lett. XXXX, XXX, XXX−XXX

Authors

Shunlong He − *School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China; College of Chemistry, Chemical Engineering and Environmental Engineering, Liaoning Shihua University, Fushun 113001, China*

Huanchao Gu − *School of Physical Science and Technology, ShanghaiTech University, Shanghai 201210, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01994

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge NSFC (Grant No. 21702138) and ShanghaiTech University start-up funding for financial support. The authors thank the support from Analytical Instrumentation Center (contract no. SPST-AIC10112914), SPST, ShanghaiTech University, and Dr. Na Yu for the X-ray crystallographic analysis.

■ REFERENCES

(1) (a) Nantermet, P. G.; Barrow, J. C.; Selnick, H. G.; Homnick, C. F.; Freidinger, R. M.; Chang, R. S. L.; O'Malley, S. S.; Reiss, D. R.; Broten, T. P.; Ransom, R. W.; Pettibone, D. J.; Olah, T.; Forray, C. Selective α1a adrenergic receptor antagonists based on 4-aryl-3,4-dihydropyridine-2-ones. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1625−1628. (b) Goodman, K. B.; Cui, H.; Dowdell, S. E.; Gaitanopoulos, D. E.; Ivy, R. L.; Sehon, C. A.; Stavenger, R. A.; Wang, G. Z.; Viet, A. Q.; Xu, W.; Ye, G.; Semus, S. F.; Evans, C.; Fries, H. E.; Jolivette, L. J.; Kirkpatrick, R. B.; Dul, E.; Khandekar, S. S.; Yi, T.; Jung, D. K.; Wright, L. L.; Smith, G. K.; Behm, D. J.; Bentley, R.; Doe, C. P.; Hu, E.; Lee, D. Development of Dihydropyridone Indazole Amides as Selective Rho-Kinase Inhibitors. *J. Med. Chem.* **2007**, *50*, 6−9. (c) Lodin-Friedman, A.; Carmeli, S. Metabolites from Microcystis aeruginosa Bloom Material Collected at a Water Reservoir near Kibbutz Hafetz Haim, Israel. *J. Nat. Prod.* **2013**, *76*, 1196−1200. (d) Lopez-Tapia, F.; Walker, K. A. M.; Brotherton-Pleiss, C.; Caroon, J.; Nitzan, D.; Lowrie, L.; Gleason, S.; Zhao, S.-H.; Berger, J.; Cockayne, D.; Phippard, D.; Suttmann, R.; Fitch, W. L.; Bourdet, D.; Rege, P.; Huang, X.; Broadbent, S.; Dvorak, C.; Zhu, J.; Wagner, P.; Padilla, F.; Loe, B.; Jahangir, A.; Alker, A. Novel Series of Dihydropyridinone P2 × 7 Receptor Antagonists. *J. Med. Chem.* **2015**, *58*, 8413−8426.

(2) (a) Behforouz, M.; Ahmadian, M. Diels−Alder Reactions of 1-Azadienes. *Tetrahedron* **2000**, *56*, 5259−5288. (b) Groenendaal, B.; Ruijter, E.; Orru, R. V. A. 1-Azadienes in cycloaddition and multicomponent reactions towards N-heterocycles. *Chem. Commun.* **2008**, 5474−5489. (c) Blond, G.; Gulea, M.; Mamane, V. Recent Contributions to Hetero Diels-Alder Reactions. *Curr. Org. Chem.* **2016**, *20*, 2161−2210.

(3) (a) Boger, D. L.; Kasper, A. M. A general solution to implementing the 4.pi. participation of 1-aza-1,3-butadienes in Diels-Alder reactions: inverse electron demand Diels-Alder reactions of.alpha..beta.-unsaturated N-benzenesulfonyl imines. *J. Am. Chem. Soc.* **1989**, *111*, 1517−1519. (b) Boger, D. L.; Corbett, W. L.; Wiggins, J. M. Room-temperature, endo-specific 1-aza-1,3-butadiene Diels-Alder reactions: acceleration of the LUMOdiene-controlled [4 + 2] cycloaddition reactions through noncomplementary aza diene substitution. *J. Org. Chem.* **1990**, *55*, 2999−3000. (c) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. Inverse electron-demand Diels-Alder reactions of N-sulfonyl.alpha.,.beta.-unsaturated imines: a general approach to implementation of the 4.pi. participation of 1-aza-1,3-butadienes in Diels-Alder reactions. *J. Am. Chem. Soc.* **1991**, *113*, 1713−1729. (d) Berry, C. R.; Hsung, R. P. Inverse electron-demand aza-[4 + 2] cycloaddition reactions of allenamides. *Tetrahedron* **2004**, *60*, 7629−7636.

(4) (a) Jiang, X.; Wang, R. Recent Developments in Catalytic Asymmetric Inverse-Electron-Demand Diels−Alder Reaction. *Chem. Rev.* **2013**, *113*, 5515−5546. (b) Masson, G.; Lalli, C.; Benohoud, M.; Dagousset, G. Catalytic enantioselective [4 + 2]-cycloaddition: a strategy to access aza-hexacycles. *Chem. Soc. Rev.* **2013**, *42*, 902−923. (c) Eschenbrenner-Lux, V.; Kumar, K.; Waldmann, H. The Asymmetric Hetero-Diels−Alder Reaction in the Syntheses of Biologically Relevant Compounds. *Angew. Chem., Int. Ed.* **2014**, *53*, 11146−11157. (d) Xie, M.; Lin, L.; Feng, X. Catalytic Asymmetric Inverse-Electron-Demand Hetero-Diels−Alder Reactions. *Chem. Rec.* **2017**, *17*, 1184−1202. (e) Dudognon, Y.; Rodriguez, J.; Constantieux, T.; Bugaut, X. Organocatalytic Enantioselective Synthesis of Tetrahydropyridines. *Eur. J. Org. Chem.* **2018**, *2018*, 2432−2442.

(5) Asymmetric [3 + 3] cycloadditions for synthesis of dihydropyridinones: (a) Yetra, S. R.; Bhunia, A.; Patra, A.; Mane, M. V.; Vanka, K.; Biju, A. T. Enantioselective N-Heterocyclic Carbene-Catalyzed Annulations of 2-Bromoenals with 1,3-Dicarbonyl Compounds and Enamines via Chiral α,β-Unsaturated Acylazoliums. *Adv. Synth. Catal.* **2013**, *355*, 1089−1097. (b) Chen, X.-Y.; Gao, Z.-H.; Song, C.-Y.; Zhang, C.-L.; Wang, Z.-X.; Ye, S. N-Heterocyclic Carbene Catalyzed Cyclocondensation of α,β-Unsaturated Carboxylic Acids: Enantioselective Synthesis of Pyrrolidinone and Dihydropyridinone Derivatives. *Angew. Chem., Int. Ed.* **2014**, *53*, 11611−11615. (c) Gao, Z.-H.; Chen, X.-Y.; Zhang, H.-M.; Ye, S. N-Heterocyclic carbene-catalyzed [3 + 3] cyclocondensation of bromoenals with aldimines: highly enantioselective synthesis of dihydropyridinones. *Chem. Commun.* **2015**, *51*, 12040−12043. (d) Xia, W.; Yao, H.; Liu, D.; Zhao, L.; Zhou, Y.; Liu, H. Enantioselective N-Heterocyclic Carbene-Catalyzed [3 + 3] Annulation of α,β-Unsaturated Esters with Methyl Ketoimine. *Adv. Synth. Catal.* **2016**, *358*, 1864−1869. (e) Chen, K.-Q.; Gao, Z.-H.; Ye, S. (Dynamic) Kinetic Resolution of Enamines/Imines: Enantioselective N-Heterocyclic Carbene Catalyzed [3 + 3] Annulation of Bromoenals and Enamines/Imines. *Angew. Chem., Int. Ed.* **2019**, *58*, 1183−1187. (f) Zhang, Z.; Zeng, X.; Xie, D.; Chen, D.; Ding, L.; Wang, A.; Yang, L.; Zhong, G. N-Heterocyclic Carbene-Catalyzed Activation of Esters of N-Hydroxyphthalimide: A Highly Enantioselective Route to Chiral Dihydropyridinones Bearing an All Carbon Quaternary Stereogenic Center. *Org. Lett.* **2015**, *17*, 5052−5055. (g) Yan, J.; Song, Z.; Zhao, C.; Shi, K.; Yang, L.; Zhong, G. Highly Chemoselective and Enantioselective Synthesis of 3,4−2H-Pyrindin-2-ones by an NHC-Catalyzed [3 + 3] Cyclization. *Org. Lett.* **2020**, *22*, 3329−3334.

(6) He, M.; Struble, J. R.; Bode, J. W. Highly Enantioselective Azadiene Diels−Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2006**, *128*, 8418−8420.

(7) Jian, T.-Y.; Shao, P.-L.; Ye, S. Enantioselective [4 + 2] cycloaddition of ketenes and 1-azadienes catalyzed by N-heterocyclic carbenes. *Chem. Commun.* **2011**, *47*, 2381−2383.

(8) (a) Jian, T.-Y.; Sun, L.-H.; Ye, S. Highly enantioselective [4 + 2] cyclization of chloroaldehydes and 1-azadienes catalyzed by N-heterocyclic carbenes. *Chem. Commun.* **2012**, *48*, 10907−10909. (b) Wang, D.-L.; Liang, Z.-Q.; Chen, K.-Q.; Sun, D.-Q.; Ye, S. Enantioselective N-Heterocyclic Carbene-Catalyzed Synthesis of Trifluoromethyldihydropyridinones. *J. Org. Chem.* **2015**, *80*, 5900−5905. (c) Liang, Z.-Q.; Wang, D.-L.; Zhang, C.-L.; Ye, S. Enantioselective N-heterocyclic carbene-catalyzed synthesis of saccharine-derived dihydropyridinones with cis-selectivity. *Org. Biomol. Chem.* **2016**, *14*, 6422−6425. (d) Rong, Z.-Q.; Wang, M.; Chow, C. H. E.; Zhao, Y. A Catalyst-Enabled Diastereodivergent Aza-Diels−Alder Reaction: Complementarity of N-Heterocyclic Carbenes and Chiral Amines. *Chem. - Eur. J.* **2016**, *22*, 9483−9487.

(9) Qian, H.; Yu, X.; Zhang, J.; Sun, J. Organocatalytic Enantioselective Synthesis of 2,3-Allenoates by Intermolecular Addition of Nitroalkanes to Activated Enynes. *J. Am. Chem. Soc.* **2013**, *135*, 18020−18023.

(10) Simal, C.; Lebl, T.; Slawin, A. M. Z.; Smith, A. D. Dihydropyridones: Catalytic Asymmetric Synthesis, N- to C-Sulfonyl

Transfer, and Derivatizations. *Angew. Chem., Int. Ed.* **2012**, *51*, 3653−3657.
(11) Young, C. M.; Stark, D. G.; West, T. H.; Taylor, J. E.; Smith, A. D. Exploiting the Imidazolium Effect in Base-free Ammonium Enolate Generation: Synthetic and Mechanistic Studies. *Angew. Chem., Int. Ed.* **2016**, *55*, 14394−14399.
(12) Jiang, J.; Qing, J.; Gong, L.-Z. Asymmetric Synthesis of 3-Amino-δ-lactams and Benzo[a]quinolizidines by Catalytic Cyclization Reactions Involving Azlactones. *Chem. - Eur. J.* **2009**, *15*, 7031−7034.
(13) Esquivias, J.; Arrayás, R. G.; Carretero, J. C. Catalytic Asymmetric Inverse-Electron-Demand Diels−Alder Reaction of N-Sulfonyl-1-Aza-1,3-Dienes. *J. Am. Chem. Soc.* **2007**, *129*, 1480−1481.
(14) (a) Han, B.; Li, J.-L.; Ma, C.; Zhang, S.-J.; Chen, Y.-C. Organocatalytic Asymmetric Inverse-Electron-Demand Aza-Diels−Alder Reaction of N-Sulfonyl-1-aza-1,3-butadienes and Aldehydes. *Angew. Chem., Int. Ed.* **2008**, *47*, 9971−9974. (b) Jiang, X.; Shi, X.; Wang, S.; Sun, T.; Cao, Y.; Wang, R. Bifunctional Organocatalytic Strategy for Inverse-Electron-Demand Diels−Alder Reactions: Highly Efficient In Situ Substrate Generation and Activation to Construct Azaspirocyclic Skeletons. *Angew. Chem., Int. Ed.* **2012**, *51*, 2084−2087.
(15) He, L.; Laurent, G.; Retailleau, P.; Folléas, B.; Brayer, J.-L.; Masson, G. Highly Enantioselective Aza-Diels−Alder Reaction of 1-Azadienes with Enecarbamates Catalyzed by Chiral Phosphoric Acids. *Angew. Chem., Int. Ed.* **2013**, *52*, 11088−11091.
(16) (a) Rajkumar, S.; Wang, J.; Zheng, S.; Wang, D.; Ye, X.; Li, X.; Peng, Q.; Yang, X. Regioselective and Enantioselective Synthesis of β-Indolyl Cyclopentenamides by Chiral Anion Catalysis. *Angew. Chem., Int. Ed.* **2018**, *57*, 13489−13494. (b) Rajkumar, S.; He, S.; Yang, X. Kinetic Resolution of Tertiary 2-Alkoxycarboxamido-Substituted Allylic Alcohols by Chiral Phosphoric Acid Catalyzed Intramolecular Transesterification. *Angew. Chem., Int. Ed.* **2019**, *58*, 10315−10319. (c) Rajkumar, S.; Wang, J.; Yang, X. Asymmetric Transformations of α-Hydroxy Enamides Catalyzed by Chiral Brønsted Acids. *Synlett* **2019**, *30*, 869−874.
(17) For a recent review on asymmetric reactions of oxazolones: (a) de Castro, P. P.; Carpanez, A. G.; Amarante, G. W. Azlactone Reaction Developments. *Chem. - Eur. J.* **2016**, *22*, 10294−10318. (b) Marra, I. F. S.; de Castro, P. P.; Amarante, G. W. Recent Advances in Azlactone Transformations. *Eur. J. Org. Chem.* **2019**, *2019*, 5830−5855. For selected examples of asymmetric cycloadditions of oxazolones: (c) Dong, S.; Liu, X.; Chen, X.; Mei, F.; Zhang, Y.; Gao, B.; Lin, L.; Feng, X. Chiral Bisguanidine-Catalyzed Inverse-Electron-Demand Hetero-Diels−Alder Reaction of Chalcones with Azlactones. *J. Am. Chem. Soc.* **2010**, *132*, 10650−10651. (d) Dong, S.; Liu, X.; Zhang, Y.; Lin, L.; Feng, X. Asymmetric Synthesis of 3,4-Diaminochroman-2-ones Promoted by Guanidine and Bisguanidium Salt. *Org. Lett.* **2011**, *13*, 5060−5063. (e) Terada, M.; Nii, H. Highly Stereoselective [4 + 2] Cycloaddition of Azlactones to β,γ-Unsaturated α-Ketoesters Catalyzed by an Axially Chiral Guanidine Base. *Chem. - Eur. J.* **2011**, *17*, 1760−1763. (f) Ying, Y.; Chai, Z.; Wang, H.-F.; Li, P.; Zheng, C.-W.; Zhao, G.; Cai, Y.-P. Bifunctional cinchona alkaloids-catalyzed asymmetric [4 + 2] cycloaddition reaction of β,γ-unsaturated α-keto esters with oxazolones. *Tetrahedron* **2011**, *67*, 3337−3342. (g) Dong, S.; Liu, X.; Zhu, Y.; He, P.; Lin, L.; Feng, X. Organocatalytic Oxyamination of Azlactones: Kinetic Resolution of Oxaziridines and Asymmetric Synthesis of Oxazolin-4-ones. *J. Am. Chem. Soc.* **2013**, *135*, 10026−10029. (h) Hejmanowska, J.; Albrecht, A.; Pięta, J.; Albrecht, Ł. Asymmetric Synthesis of 3,4-Dihydrocoumarins Bearing an α,α-Disubstituted Amino Acid Moiety. *Adv. Synth. Catal.* **2015**, *357*, 3843−3848. (i) Hu, H.; Liu, Y.; Guo, J.; Lin, L.; Xu, Y.; Liu, X.; Feng, X. Enantioselective synthesis of dihydrocoumarin derivatives by chiral scandium(iii)-complex catalyzed inverse-electron-demand hetero-Diels−Alder reaction. *Chem. Commun.* **2015**, *51*, 3835−3837. (j) Zhang, S.-Y.; Lv, M.; Yin, S.-J.; Li, N.-K.; Zhang, J.-Q.; Wang, X.-W. Asymmetric Synthesis of Dihydrocoumarins Containing Contiguous Quaternary and Tertiary Stereogenic Centers Catalyzed by a Cinchona-Alkaloid-Based Bifunctional Thiourea Derivative. *Adv. Synth. Catal.* **2016**, *358*, 143−153. (k) Zhang, Y.-C.; Zhu, Q.-N.; Yang, X.; Zhou, L.-J.; Shi, F. Merging Chiral Brønsted Acid/Base Catalysis: An Enantioselective [4 + 2] Cycloaddition of o-Hydroxystyrenes with Azlactones. *J. Org. Chem.* **2016**, *81*, 1681−1688. (l) Zhou, J.; Wang, M.-L.; Gao, X.; Jiang, G.-F.; Zhou, Y.-G. Bifunctional squaramide-catalyzed synthesis of chiral dihydrocoumarins via ortho-quinone methides generated from 2-(1-tosylalkyl)phenols. *Chem. Commun.* **2017**, *53*, 3531−3534. (m) Ma, C.; Zhou, J.-Y.; Zhang, Y.-Z.; Mei, G.-J.; Shi, F. Catalytic Asymmetric [2 + 3] Cyclizations of Azlactones with Azonaphthalenes. *Angew. Chem., Int. Ed.* **2018**, *57*, 5398−5402. (n) Ruan, S.; Lin, X.; Xie, L.; Lin, L.; Feng, X.; Liu, X. Asymmetric synthesis of 3-amino-dihydrocoumarins via the chiral guanidine catalyzed cascade reaction of azlactones. *Org. Chem. Front.* **2018**, *5*, 32−35. (o) Jensupakarn, N.; Gleeson, M. P.; Gleeson, D.; Boonyarattanakalin, K. Theoretical Investigation of the Enantioselective [4 + 2] Cycloaddition Reaction of o-Hydroxystyrene and Azlactone. *J. Org. Chem.* **2019**, *84*, 4025−4032. (p) Simlandy, A. K.; Ghosh, B.; Mukherjee, S. Enantioselective [4 + 2]-Annulation of Azlactones with Copper-Allenylidenes under Cooperative Catalysis: Synthesis of α-Quaternary α-Acylaminoamides. *Org. Lett.* **2019**, *21*, 3361−3366.
(18) For pioneer works of asymmetric chiral phosphoric acid catalysis: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-Type Reaction Catalyzed by a Chiral Brønsted Acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568. (b) Uraguchi, D.; Terada, M. Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357. For recent reviews on asymmetric CPA catalysis: (c) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744−5758. (d) Terada, M. Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Carbon-Carbon Bond Forming Reactions. *Synthesis* **2010**, *2010*, 1929−1982. (e) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete Field Guide to Asymmetric BINOL-Phosphate Derived Brønsted Acid and Metal Catalysis: History and Classification by Mode of Activation; Brønsted Acidity, Hydrogen Bonding, Ion Pairing, and Metal Phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153. (f) Akiyama, T.; Mori, K. Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115*, 9277−9306. (g) Li, X.; Song, Q. Recent advances in asymmetric reactions catalyzed by chiral phosphoric acids. *Chin. Chem. Lett.* **2018**, *29*, 1181−1192. (h) Rahman, A.; Lin, X. Development and application of chiral spirocyclic phosphoric acids in asymmetric catalysis. *Org. Biomol. Chem.* **2018**, *16*, 4753−4777.
(19) CPA catalyzed asymmetric reactions of N−H imines: (a) Miyagawa, M.; Yoshida, M.; Kiyota, Y.; Akiyama, T. Enantioselective Friedel−Crafts Alkylation Reaction of Heteroarenes with N-Unprotected Trifluoromethyl Ketimines by Means of Chiral Phosphoric Acid. *Chem. - Eur. J.* **2019**, *25*, 5677−5681. (b) Nguyen, T. B.; Bousserouel, H.; Wang, Q.; Guéritte, F. Chiral Phosphoric Acid-Catalyzed Enantioselective Transfer Hydrogenation of ortho-Hydroxyaryl Alkyl N−H Ketimines. *Org. Lett.* **2010**, *12*, 4705−4707. (c) Yonesaki, R.; Kondo, Y.; Akkad, W.; Sawa, M.; Morisaki, K.; Morimoto, H.; Ohshima, T. 3-Mono-Substituted BINOL Phosphoric Acids as Effective Organocatalysts in Direct Enantioselective Friedel−Crafts-Type Alkylation of N-Unprotected α-Ketiminoester. *Chem. - Eur. J.* **2018**, *24*, 15211−15214. (d) Vugts, D. J.; Koningstein, M. M.; Schmitz, R. F.; de Kanter, F. J. J.; Groen, M. B.; Orru, R. V. A. Multicomponent synthesis of dihydropyrimidines and thiazines. *Chem. - Eur. J.* **2006**, *12*, 7178−7189.
(20) For details, see Supporting Information.
(21) Interestingly, using the β-monosubstituted α,β-unsaturated *N*-Bz imine or 3-amido allylic secondary alcohol as coupling partners with oxazolones under the standard conditions provided the *N*-1-benzoylated dihydropyridinone products with poor to moderate diastereo- and enantioselectivities (see Scheme S1 in SI), which indicated two distinct reaction mechanisms with 3-amido allylic tertiary alcohols and their secondary alcohol analogues.
(22) Rueping, M.; Vila, C.; Uria, U. Direct Catalytic Azidation of Allylic Alcohols. *Org. Lett.* **2012**, *14*, 768−771.

https://dx.doi.org/10.1021/acs.orglett.0c01994
Org. Lett. XXXX, XXX, XXX−XXX

(23) Kwon, Y.; Jeon, M.; Park, J. Y.; Rhee, Y. H.; Park, J. Synthesis of 1H-azadienes and application to one-pot organic transformations. *RSC Adv.* **2016**, *6*, 661−668.
(24) Rajkumar, S.; Tang, M.; Yang, X. Chiral Phosphoric Acid Catalyzed Kinetic Resolution of 2-Amido Benzyl Alcohols: Asymmetric Synthesis of 4H-3,1-Benzoxazines. *Angew. Chem., Int. Ed.* **2020**, *59*, 2333−2337.
(25) A stepwise cycloaddition mechanism involving a cascade Michael addition step followed by lactamization can not be completely excluded, but a concerted cycloaddition mechanism was preferred because of the excellent diastereoselectivities observed (even for the Et/Me disubstituted product **3y**) .
(26) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. Ag-Catalyzed Asymmetric Mannich Reactions of Enol Ethers with Aryl, Alkyl, Alkenyl, and Alkynyl Imines. *J. Am. Chem. Soc.* **2004**, *126*, 3734−3735.

https://dx.doi.org/10.1021/acs.orglett.0c01994
Org. Lett. XXXX, XXX, XXX−XXX