Highly Chemoselective and Enantioselective Synthesis of 3,4-2H-Pyrindin-2-ones by an NHC-Catalyzed [3 + 3] Cyclization

Jun Yan,† Zhaoxin Song,† Chengtao Zhao, Kuangxi Shi, Limin Yang,* and Guofu Zhong*

Cite This: Org. Lett. 2020, 22, 3329–3334

ABSTRACT: A highly chemoselective and enantioselective cyclization of γ-chloroenals and ketimines has been developed to synthesize enantiopure 3,4-2H-pyrindin-2-ones as major products. It is proposed that the intermediate enone IV reacted with an enamine to proceed with a [3 + 3] cyclization, thereby affording 3,4-2H-pyrindin-2-ones as major products. Interestingly, the addition of LiCl promoted the formation of the enamine and accelerated the [3 + 3] cyclization. In contrast, the [4 + 2] cycloaddition reaction between the intermediate vinyl enolate VIII and an imine offered 5,6-2H-pyrindin-2-ones as minor products. This protocol represents the exceptional potential of N-heterocyclic carbene (NHC) catalytic reactions in accessing biologically active 3,4-2H-pyrindin-2-one derivatives in good yield with high chemoselectivities and excellent enantiomeric purities.

S

since the isolation and characterization of 1,3-di-1-adamantyl-imidazol-2-ylidene in 1991, N-heterocyclic carbenes (NHCs) in catalytic transformations have been developed not only as ligands in organometallic catalysis but also as organocatalysts. One example of an NHC-organocatalyzed reaction is the use of an umpolung to turn an aldehyde carbonyl carbon from being electrophilic to nucleophilic. Recently, there were some reports on NHC-organocatalyzed direct asymmetric α-carbon functionalization, β-carbon activations, and γ-carbon functionalization. The generation of these corresponding intermediates from active compounds, such as aldehydes, enals, ketenes, α-bromoenals, and ynals, has been revealed. As for the β-carbon functionalization, besides the homoenoled intermediate (d3 nucleophile), the enone species (a3 electrophile) has emerged as an attractive intermediate. A pioneering application of the enone species was reported by Townsend in the biosynthesis of the potent β-lactamase inhibitor clavulanic acid. In particular, the conjugate addition of l-arginine to an enone intermediate derived from NHC organocatalysis was achieved. After that, some work was reported with the generation of such species from enals, ynals, aldehydes, and α,β-unsaturated acid (derivatives). However, to the best of our knowledge, the NHC-catalyzed generation of an enone or vinyl enolate intermediate from an aldehyde has not been achieved.

3,4-2H-Pyrindin-2-ones are moieties of natural products and basic building blocks in therapeutic and synthetic chemistry. The carboxamide derivatives present bioactivities as α1-adrenergic receptor antagonists, Rho-kinase inhibitors, P2X7 receptor antagonists, or G-protein-coupled kinase receptor antagonists. Besides, these structures can be efficiently transformed into other relevant compounds like 1,4-2H-pyrindines and 1,5-benzodiazepine-1,4-2H-pyridine derivatives. Thus the construction of optically active 3,4-2H-pyrindin-2-one has attracted considerable attention.

In previous studies, we revealed a series of NHC-catalyzed asymmetric cycloaddition reactions for the construction of potentially biologically active skeletons, such as hetero-Diels–Alder reactions constructing fused pyran[2,3-b]indoles, [3 + 3] cycloaddition reactions affording a-amino acid derivatives, [3 + 2] cycloaddition reactions offering spirocyclic oxindoles, and bicyclic pyrazolidinones derivatives. We also reported the generation and application of nucleophilic vinyl enolate intermediates in the NHC-catalyzed [4 + 2] annulation reaction of γ-haloenals and isatins (Scheme 1a). Therefore, our ongoing interest in NHC catalytic cycloaddition reactions inspired us to design the construction of 5,6-2H-pyrindin-2-one skeletons with a quaternary stereogenic carbon center via the [4 + 2] cycloaddition reaction between an intermediate vinyl enolate VIII and an imine (Scheme 1b).

The chemistry described here builds on the unexpected formation of 3,4-2H-pyrindin-2-one derivatives via the [3 + 3] cyclization of the intermediate enone IV and enamines.

Received: February 23, 2020
Published: March 11, 2020
Scheme 1. Chemoselectivity of the Cyclization

Previous work:

Chemoselectivity in this work:

(Scheme 1c). In previous research work, an enone intermediate (Michael acceptor) was generated from the addition of NHC to saturated enals, oxindole-derived enals, or N-hydroxyphthalimide (NHPI) acrylates under suitable reaction conditions. Herein we report the NHC-catalyzed [3 + 3] cyclization reaction involving enone intermediates generated from γ-chloroenal to synthesize 3,4-2H-pyrindin-2-one derivatives as major products (Scheme 1c).

Our proposed catalytic cycle for the intermediate enone IV participating in the [3 + 3] cycloaddition reaction is shown in Figure 1. First, NHC nucleophilic attack on γ-chloroenal offered a zwitterion I. Second, Breslow intermediate II was rendered via a 1,2-H migration from carbon to oxygen. Third, following C–Cl bond cleavage, the Breslow intermediate II tautomerized to enone III. Fourth, the enolene–enone rearrangement via a 1,5-H shift generated intermediate enone IV. Subsequent Michael addition of intermediate enone IV with an enamine gave ketone intermediate V, thereby accompanying the loss of a proton and tautomerization to intermediate VI. Thereafter, the catalyst was generated and 3,4-2H-pyrindin-2-one was produced (Scheme 1c). Advantageously, the elimination of HCl by an external base was easily achieved by the ketone intermediate V, thereby resulting in the loss of HCl and the formation of intermediate VI. It was also possible for the intermediate enone IV to release HCl and generate vinyl enolate VIII, which can undergo a [4 + 2] cycloaddition reaction with an imine to afford a 5,6-2H-pyrindin-2-one derivative (Scheme 1b).

To examine the unprecedented NHC-catalyzed [3 + 3] cyclization between a γ-haloenal and a ketimine, we commenced our studies by readily prepared γ-haloenal 1a and ketimine 2a with optically pure N-substituted triazolium salts using different bases and different solvents (Table 1). When triazolium salt A with an N-mesityl group was chosen as a precatalyst with Cs2CO3 in toluene, a 3,4-2H-pyrindin-2-one skeleton was constructed with great enantioselectivity (96% ee), albeit with a low yield (25%) and moderate chemoselectivity (6:1) (entry 1). The precatalyst with an N-phenyl group could also afford the desired product with bad results (80% ee, 5:1 chemoselectivity, and 21% yield) (entry 2).

After carrying out the solvent screening, diethyl ether was found to be the best solvent (entry 6), with dramatically increased yield (60%), better chemoselectivity (7:1), and the highest enantioselectivity (>99% ee). Accordingly, different bases were evaluated using diethyl ether and N-mesityl triazolium salt A. When a base such as Na2CO3, K2CO3, DMAP, Et3N, or DABCO was employed, the yield of 3,4-2H-pyrindin-2-one decreased to 31–53% with comparable enantioselectivities (95–98% ee) (entries 8–12). When a Lewis acid such as LiCl was added into the reaction, the chemoselectivity increased dramatically from 7:1 to 12:1 with excellent yield and enantioselectivity (entry 14). Notably, the yield and enantioselectivity obtained were the highest when LiCl was used (entry 14). In contrast, the use of a Brønsted acid such as pivalic acid did not enhance the formation of a [3 + 3] adduct, as demonstrated by a significantly lower chemoselectivity of 8:1 (entry 16). The control experiments showed that the addition of LiCl could promote the formation of enamine (for details, see the SI), thereby accelerating the β-activation [3 + 3] cyclization.

Having established this optimal reaction condition, the substrate scope of the reaction between γ-chloroenal 1 and ketimine 2 was investigated as illustrated in Scheme 2. Pleasingly, a variety of substitutions on the phenyl ring of ketimine 2 were shown to participate in the [3 + 3] cycloaddition reaction with γ-chloro-β-phenylbut-2-enal 1a to afford 3,4-2H-pyrindin-2-one derivatives in high yield and with excellent optical purities (98 to >99% ee, up to >19:1 chemoselectivity). The cyclization proceeded consistently for ketimines carrying an electron-withdrawing group (Scheme 2e–g, 2h). Similarly, electron-donating substituted ketimines were well-accommodated, with para-methyl and para-isopropyl providing 3,4-dihydropyrindin-2-ones with the highest enantioselectivity (>99% ee) and with high chemoselectivities (11:1), albeit with relatively lower yields (3e and 3f). The electron-donating substitutions on the phenyl ring of ketimines would discourage the formation of enamines and thus decrease the yield. Increased chemoselectivity and undiminished enantioselectivity and yield were
observed when the electronegativity of the substituent on the phenyl ring of the ketimine was changed from para-fluoro, to para-chloro, to para-bromo (3b–d). In addition, high yields and good optical purities were obtained regardless of the use of an ortho, meta, or para substituent on the phenyl ring of the ketimine (3c, 3g, and 3h). Notably, the use of the ortho-substituent on the phenyl ring of the ketimine resulted in a high chemoselectivity. Accordingly, ortho-chlorophenyl ketimine afforded 3,4-dihydropyrindin-2-one (3h) with the highest enantioselectivity (99% ee), the best yield (83%), and the highest chemoselectivity (19:1).

We then investigated the scope of the γ-chloroenal component in the construction of 3,4-2H-pyrindin-2-one skeletons. Absolute configurations of major enantiomers were assigned based on the X-ray crystallographic analysis of product 3n. (For details, see the SI.) In general, the corresponding products were obtained in good yield with high enantioselectivities. It was observed that the electronic properties of substituents on the para position of the phenyl ring affected the yield rather than the enantioselectivity of the corresponding product. For instance, γ-chloroenals with an electron-deficient substituent on the para position of the phenyl ring smoothly reacted with 2a, affording 3,4-2H-pyrindin-2-ones as main products in good yield (51–71%) with high regioselectivities (10:1 to 11:1) and high enantioselectivities (98 to >99% ee) (3i–k, 3n). Replacement of the electron-deficient substituent with an electron-rich substituent also led to the corresponding products with high enantioselectivities, albeit with lower yields (3l, 55% yield, 10:1 chemoselectivity, >99% ee; 3m, 60% yield, 11:1 regioselectivity, >99% ee). Furthermore, the position of the substituent on the phenyl ring of the γ-chloroenals influenced the yield instead of the regioselectivities and enantiopurities (3j and 3o). For instance, the use of a meta-chloro-substituted phenyl ring on the γ-chloroenal provided 3,4-dihydropyrindin-2-one with a lower yield (41%), the same regioselectivity (10:1), and similar enantiomeric purity (>99% ee) as the para-substituent. Naphthalen-2-yl- and thiophen-2-yl-substituted γ-chloroenal were also employed in the reaction, thereby affording the desired products (3p–q) with high chemoselectivities and enantioselectivities despite lower yields.

Furthermore, we demonstrated the synthetic utility of this [3 + 3] cyclization by transforming the 3,4-2H-pyrindin-2-one products to other useful moieties with simple protocols. For instance, treatment with diphenyl chlorophosphate at −78 °C in THF successfully converted optically pure 3,4-2H-pyrindin-2-one 3a to the corresponding phosphoric ester 5a without the loss of enantioselectivity in modest yield (61% yield and >99% ee, Scheme 3).

To explore the origins of stereoselectivity, density functional theory (DFT) calculations (at the wB97xd/6-311++G(d,p), SMD (diethyl ether)//wB97xd/6-31G(d)/6-31G(d), and SMD (diethyl ether) levels of theory) were performed with the Gaussian 09 package. On the basis of our calculation, trans-enone a is the most stable conformer for the cyclization with enamine. The stereochemistry of the final [3 + 3] cyclization
product is determined by the relative transition state for the unblocked re face or si face addition of the enamine to the most stable trans-enone (Figure 2). It is obvious that trans-enone a is a predistorted structure for the transition state by leaving the si face unblocked. TSa was formed by distorting the 30° dihedral angle $\angle N1-C1-C2-C3$ and led to an R enantiomer. In contrast, to leave the re face available for TSb, cis-a needs to distort a 125° dihedral angle. Thus the distortion energy of the enone fragment in TSb is larger than that in TSa by 1.9 kcal/mol. For enamine, the dihedral angle $\angle C1-S1-N1-C2$, which is 63° for the ground state and 65° for the transition structure TSa, is distorted to 44° in the structure of TSb. Therefore, the distortion energy of the enamine fragment in TSb is more than that for TSa by 0.6 kcal/mol. The interaction energies for TSa and TSb are almost the same. Comparing the activation energies for TSb and TSa, there is a 2.6 kcal/mol reduction. The DFT calculation shows that TSa is the favorable transition state and is more stable than TSb, with 3.0 kcal/mol free-energy difference (99% ee in calculation). The computational results are consistent with the experimental observations.

In conclusion, we investigated the highly chemoselective and stereoselective NHC-catalyzed [3 + 3] cyclization. Consequently, pure 3,4-2H-pyridin-2-ones were obtained, accompanied by very small amounts of 5,6-2H-pyridin-2-ones. It is proposed that an enone intermediate is generated by $\beta$-activation, which dominates the chemoselectivities of the [3 + 3] cycloaddition over a vinyl enolate intermediate.
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**

Limin Yang — College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China; orcid.org/0000-0003-1021-3942; Email: myang@hznu.edu.cn

Guofu Zhong — College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China; orcid.org/0000-0001-9497-9069; Email: zgfi@hznu.edu.cn

**Authors**

Jun Yan — College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China

Zhaoxin Song — College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China

Chengtao Zhao — College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China

Kuangxi Shi — College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 311121, China

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00699

**Author Contributions**

†J.Y. and Z.S. contributed equally.

**Notes**

The authors declare no competing financial interest.

**ACKNOWLEDGMENTS**

We gratefully acknowledge the National Natural Science Foundation of China (NSFC) (nos. 21302032, 21373073, and 21672048), the Natural Science Foundation of Zhejiang Province (ZJNSF) (no. LY20B020010), and the PCSIRT (no. IRT 1231) for financial support. G.Z. acknowledges a Qianjiang Scholar award from Zhejiang Province in China. The cover was conceived by Limin Yang and Guofu Zhong and created by Fang Liu from DesignOne with assistance by Jun Yan.

**REFERENCES**


