Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2019, **10**, 9853

All publication charges for this article have been paid for by the Royal Society of Chemistry

Enantioselective synthesis of quaternary 3,4-dihydroisoquinolinones *via* Heck carbonylation reactions: development and application to the synthesis of Minalrestat analogues†

Cang Cheng, Bin Wan, Bo Zhou, Yichao Gu and Yanghui Zhang *

Received 10th July 2019
Accepted 31st August 2019

DOI: 10.1039/c9sc03406d

rsc.li/chemical-science

Minalrestat and its analogues represent structurally novel aldose reductase inhibitors, and the asymmetric synthesis of such pharmaceutically privileged molecules has not been reported yet. We have developed a palladium-catalyzed enantioselective intramolecular carbonylative Heck reaction by using formate esters as the source of CO, which represents the first enantioselective synthesis of quaternary 3,4-dihydroisoquinolines. The reaction provides a facile and efficient method for the synthesis of enantiopure nitrogen-containing heterocyclic compounds bearing an all-carbon quaternary stereocenter. The reaction has been successfully applied to the first asymmetric synthesis of Minalrestat analogues.

Introduction

Diabetes mellitus is a major health concern and affects millions of people worldwide.[1] Aldose reductase inhibitors (ARIs) are attractive therapeutic targets for designing drugs to prevent or slow the progression of diabetic complications.[2] Although various ARIs have been discovered, almost all of them have been withdrawn due to adverse side effects or low efficacy.[3] Minalrestat is an important ARI that shows appreciable activity and safety profiles and is a promising drug candidate.[4] Minalrestat is a 3,4-dihydroisoquinolinone derivative bearing a spirosuccinimide moiety at the 4-position (Fig. 1). Actually, the isoquinolinone backbone in Minalrestat represents a structurally novel framework for designing potent ARIs, and a range of derivatives derived from the backbone exhibit intrinsic activity and good oral potency.[4] Notably, these bioactive isoquinolinone derivatives usually contain a quaternary carbon stereocenter, and the stereocenter plays crucial roles in the bioactivities and oral potency. Unfortunately, the stereocenters tend to racemize *via* enolization.[4a] The asymmetric synthesis of this isoquinolinone skeleton is not available,[5] and the enantiopure compounds were obtained by the resolution of racemates.[4a] Therefore, it is a formidable task to develop enantioselective reactions for the construction of such six-membered isoquinolinones containing an all-carbon quaternary stereocenter, which would allow us to not only obtain enantiopure compounds for drug discovery but also modify the structures to prevent racemization.

3,4-Dihydroisoquinolinone skeletons are widely found in natural products and are pivotal structural motifs in drug molecules,[6] and many of the bioactive 3,4-dihydroisoquinolinone derivatives contain an all-carbon quaternary stereocenter at the 4-position[7] (Fig. 1). As such, asymmetric reactions for the construction of such isoquinolinone skeletons would find wide applications in organic synthesis. Although

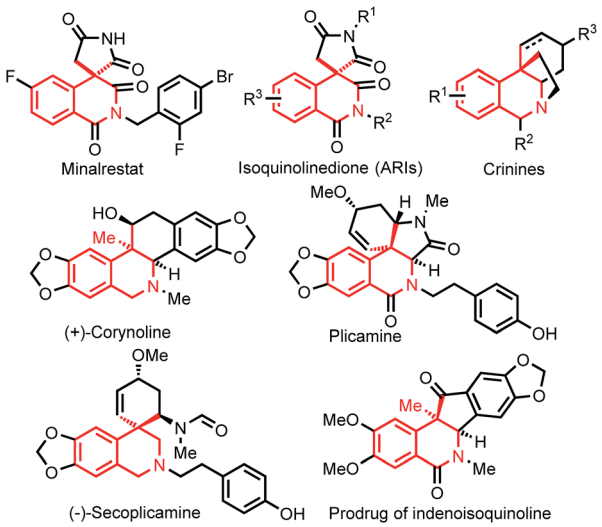


Fig. 1 Bioactive 3,4-dihydroisoquinolinone derivatives containing all-carbon quaternary stereocenters at the 4-position.

School of Chemical Science and Engineering, Shanghai Key Laboratory of Chemical Assessment and Sustainability, Tongji University, 1239 Siping Road, Shanghai 200092, China. E-mail: zhangyanghui@tongji.edu.cn

† Electronic supplementary information (ESI) available: Full experimental details and characterisation. CCDC 1921698. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc03406d

编号：2020TJJS150522

证　　明

经检索 Science Citation Index Expanded (SCI-EXPANDED)数据库、Journal Citation Reports (JCR) 数据库，同济大学化学科学与工程学院程沧的如下 1 篇论文被 SCI 收录，并附最新（2018）期刊影响因子。

详细如下：

第 1 条，共 1 条

标题: Enantioselective synthesis of quaternary 3,4-dihydroisoquinolinones via Heck carbonylation reactions: development and application to the synthesis of Minalrestat analogues

作者: Cheng, C (Cheng, Cang); Wan, B (Wan, Bin); Zhou, B (Zhou, Bo); Gu, YC (Gu, Yichao); Zhang, YH (Zhang, Yanghui)

来源出版物: CHEMICAL SCIENCE **卷:** 10 **期:** 42 **页:** 9853-9858 **DOI:** 10.1039/c9sc03406d **出版年:** NOV 14 2019

Web of Science 核心合集中的 "被引频次": 3

被引频次合计: 3

入藏号: WOS:000493521200023

文献类型: Article

地址: [Cheng, Cang; Wan, Bin; Zhou, Bo; Gu, Yichao; Zhang, Yanghui] Tongji Univ, Shanghai Key Lab Chem Assessment & Sustainabil, Sch Chem Sci & Engn, 1239 Siping Rd, Shanghai 200092, Peoples R China.

通讯作者地址: Zhang, YH (通讯作者)，Tongji Univ, Shanghai Key Lab Chem Assessment & Sustainabil, Sch Chem Sci & Engn, 1239 Siping Rd, Shanghai 200092, Peoples R China.

电子邮件地址: zhangyanghui@tongji.edu.cn

ISSN: 2041-6520

eISSN: 2041-6539

期刊影响因子（2018 年）：9.556

期刊 JCR 分区：

JCR® 类别	*类别中的排序*	*JCR 分区*
CHEMISTRY, MULTIDISCIPLINARY	**19/172**	**Q1**

数据来自第 2018 版 Journal Citation Reports

特此证明！

同济大学科技情报所

检索人：郑晓云

2020 年 06 月 24 日

OL | Organic Letters

pubs.acs.org/OrgLett Letter

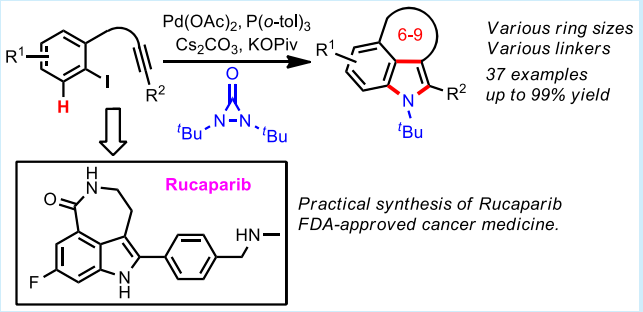
Synthesis of 3,4-Fused Tricyclic Indoles through Cascade Carbopalladation and C−H Amination: Development and Total Synthesis of Rucaparib

Cang Cheng, Xiang Zuo, Dongdong Tu, Bin Wan, and Yanghui Zhang*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01513 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: 3,4-Fused tricyclic indole scaffolds are ubiquitous in bioactive natural products and pharmaceuticals. A new protocol for the synthesis of 3,4-fused tricyclic indoles has been developed through cascade carbopalladation and C−H amination with *N,N*-di-*tert*-butyldiaziridinone. The protocol allows access to a range of 3,4-fused tricyclic indoles, including those containing various linkers and fused with medium-sized rings. Rucaparib can be synthesized via this reaction, providing an advantageous synthetic method for the FDA-approved cancer medicine.



3,4-Fused tricyclic indoles are essential core structures of many bioactive natural products and pharmaceuticals and are attractive synthetic targets in the fields of medicinal chemistry and organic synthesis (Figure 1)[1] The synthesis of these

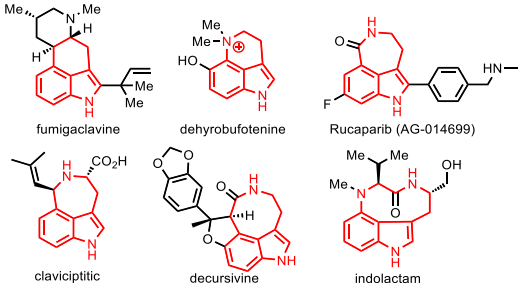


Figure 1. Selected examples of 3,4-fused tricyclic indoles.

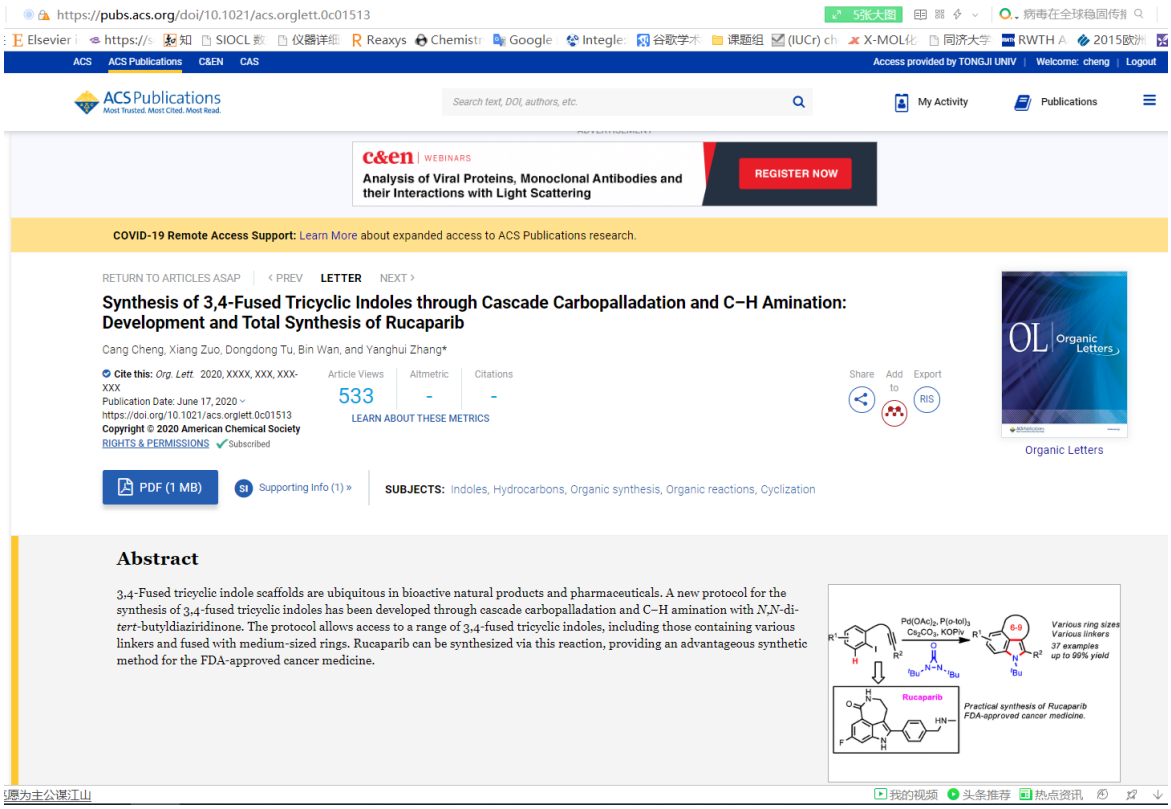
complex indole molecules is challenging and has been the subject of numerous synthetic studies.[2] Traditionally, 3,4-fused tricyclic indoles can be synthesized by the intramolecular cyclization of 4-substituted or 3,4-disubstituted indoles. However, the functionalization of the four-positions of indoles is challenging and usually requires multistep synthesis. Recently, the construction of 3,4-fused tricyclic indoles via indole ring formation has gained considerable interest. Compared with the traditional methods, this innovative approach avoids the laborious synthesis of four-substituted indole precursors and has great advantages. An elegant example is the method based on an intramolecular Fischer indole synthesis, which was developed by Cho and coworkers.[3] In 2013, the groups of Boger and Jia reported the synthesis of 3,4-fused tricyclic indoles using alkyne-tethered *ortho*-iodoanilines via palladium-catalyzed intramolecular Larock indole synthesis.[4] Replacing the alkyne moiety with an allene group can also give 3,4-fused tricyclic indoles.[5] The intramolecular Larock indole syntheses require the presynthesis of multisubstituted haloanilines as starting materials. Notably, an innovative method through C−H alkenylation using anilines tethered to an alkyne at the meta position has been independently developed by the groups of Jia, Xu and Liu, Zhou and Li, and Nemoto.[6] However, to activate more hindered C−H bonds, the reactions are restricted to indoles bearing an alkoxy group.[2a] The group of Miura and Murakami disclosed an elegant dearomatizing annulation reaction from 1,2,3-triazole-tethered arenes.[7] However, this method requires an additional oxidation reaction to form indole products and the presynthesis of 1,2,3-triazole-containing substrates. In all of these reactions, 3,4-fused tricyclic indoles are directly formed from the intramolecular cyclization of the substrates, and all of the substrates preinstalled with a nitrogen-containing group are used.[8] Considerable efforts should still be devoted to developing efficient and general methods for the synthesis of 3,4-fused tricyclic indoles.

Over the past several decades, transition-metal-catalyzed C−H functionalization underwent explosive growth.[9] C−H

Received: May 2, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01513
Org. Lett. XXXX, XXX, XXX−XXX

网页检索证明


https://pubs.acs.org/doi/10.1021/acs.orglett.0c01513
ACS Publications
Most Trusted. Most Cited. Most Read.
Search text, DOI, authors, etc.
My Activity
Publications
c&en | WEBINARS
Analysis of Viral Proteins, Monoclonal Antibodies and their Interactions with Light Scattering
REGISTER NOW
COVID-19 Remote Access Support: Learn More about expanded access to ACS Publications research.
RETURN TO ARTICLES ASAP
< PREV
LETTER
NEXT >
Synthesis of 3,4-Fused Tricyclic Indoles through Cascade Carbopalladation and C–H Amination: Development and Total Synthesis of Rucaparib
Cang Cheng, Xiang Zuo, Dongdong Tu, Bin Wan, and Yanghui Zhang*
Cite this: Org. Lett. 2020, XXXX, XXX, XXX-XXX
Publication Date: June 17, 2020
https://doi.org/10.1021/acs.orglett.0c01513
Copyright © 2020 American Chemical Society
RIGHTS & PERMISSIONS
Subscribed
Article Views
533
Altmetric
-
Citations
-
LEARN ABOUT THESE METRICS
Share
Add to
Export
RIS
OL Organic Letters
Organic Letters
PDF (1 MB)
Supporting Info (1) »
SUBJECTS: Indoles, Hydrocarbons, Organic synthesis, Organic reactions, Cyclization
Abstract
3,4-Fused tricyclic indole scaffolds are ubiquitous in bioactive natural products and pharmaceuticals. A new protocol for the synthesis of 3,4-fused tricyclic indoles has been developed through cascade carbopalladation and C–H amination with N,N-di-tert-butyldiaziridinone. The protocol allows access to a range of 3,4-fused tricyclic indoles, including those containing various linkers and fused with medium-sized rings. Rucaparib can be synthesized via this reaction, providing an advantageous synthetic method for the FDA-approved cancer medicine.
Pd(OAc)2, P(o-tol)3
Cs2CO3, KOPiv
6-9
Various ring sizes
Various linkers
37 examples
up to 99% yield
Rucaparib
Practical synthesis of Rucaparib
FDA-approved cancer medicine.