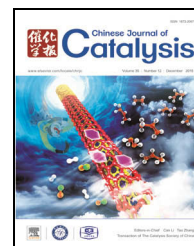


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Article

Co(III)/Zn(II)-catalyzed dearomatization of indoles and coupling with carbenes from ene-yne ketones via intramolecular cyclopropanation



Na Li^{a,b}, Junbiao Chang^{a,*}, Lingheng Kong^c, Shuangjing Wang^a, Dandan Wang^a, Miao Cheng^a, Xingwei Li^{a,c,#}

^a Henan Key Laboratory of Organic Functional Molecule and Drug Innovation, School of Chemistry and Chemical Engineering, Henan Normal University, Xixiang 453007, Henan, China

^b School of Pharmacy, Xixiang Medical University, Xixiang 453003, Henan, China

^c Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China

ARTICLE INFO

Article history:

Received 21 June 2018

Accepted 26 July 2018

Published 5 December 2018

Keywords:

Co(III)/Zn(II) catalysis

Dearomatization

Cyclopropanation

Carbene

Indole

ABSTRACT

A straightforward and efficient protocol for dearomatizing indoles is described. The reaction, catalyzed by an inexpensive Co(III)/Zn(II) catalyst, starts from easily accessible *N*-pyrimidinyl indoles and ene-yne ketones. Mild reaction conditions, high diastereoselectivity, a broad substrate scope, effective functional group tolerance, and reasonable to remarkable yields were observed.

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1. Introduction

Indoline skeletons have been considered as characteristic structures owing to their widespread use as key building blocks and chiral auxiliaries in asymmetric synthesis [1]. They are also widely present in alkaloids and other natural products with diverse biological activities [2–9], such as pentopril, which is a potent angiotensin enzyme inhibitor [3], strychnine, which is used as a pesticide [2], and lundurine A, which is effective for overcoming multidrug resistance in vincristine-resistant KB cells (Fig. 1) [10–12]. Chiral cyclopropanes are important mo-

tifs for the diverse functionality and reactivity provided by donor-acceptor substituents, which can be transformed into valuable synthetic intermediates via ring opening or ring expansion [13–20]. A hexacyclic ring system that includes a unique cyclopropyl ring fused to an indoline accompanied by three quaternary carbon stereocenters such as lundurines are attractive targets. Traditional methods to construct cyclopropane-fused indoline derivatives include transition-metal-mediated reactions [21–36], the classic Simmons-Smith reaction and so on [34–41]. However, highly efficient, environmentally friendly, and atom-economic methods

* Corresponding author. Tel: +86-411-84379089; E-mail: changjunbiao@zzu.edu.cn

Corresponding author. Tel: +86-411-84379089; E-mail: xwli@dicp.ac.cn

This work was supported by the National Natural Science Foundation of China (21525208, 21472186) and the research fund from Henan Normal University (5101034011009).

DOI: 10.1016/S1872-2067(18)63154-7 | <http://www.sciencedirect.com/science/journal/18722067> | Chin. J. Catal., Vol. 39, No. 12, December 2018

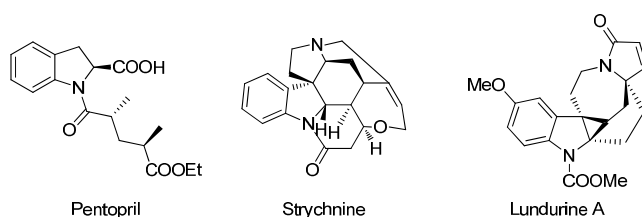
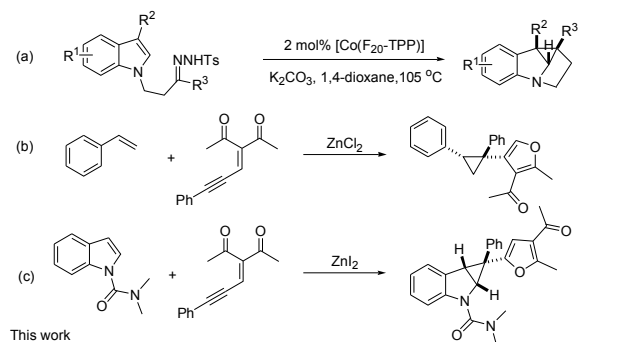


Fig. 1. Some examples of bioactive indolines.

for generating available carbenoids precursors in a catalytic fashion continue to be highly limited [42]. The catalytic generation of M-furylcarbenes derived from carbonyl ene-yne compounds and zinc salts were explored for its versatile character [43–48]. Che et al. [21] reported cobalt(II) porphyrin-catalyzed intramolecular cyclopropanation of *N*-alkyl indoles/pyrroles with alkyldiazomethanes generated in situ from hydrazones (Scheme 1(a)). Lopez et al. [47] reported the catalytic generation of zinc(II) furylcarbenes derived from carbonyl ene-yne compounds and zinc salts, as well as their reactivity in addition and insertion processes with styrene (Scheme 1(b)). Recently, while collating the data for the present article, Xu et al. [49] explored the access to similar products via ZnI₂-catalyzed cyclopropanation of indole with enynone. Notwithstanding the success, the investigation is limited to low functional group tolerance; certain *N*-substituent of indole failed to generate the desired product (Scheme 1(c)). As well-established and efficient catalysts for various organic transformations, Cp*Co(III) complexes have attracted increasing attention owing to their earth-abundance, cost-effectiveness, low toxicity, and unique catalytic reactivity [50–55]. However, the catalytic generation of efficient cyclopropanating intermediates from ene-yne ketone and Co(III)/Zn(II) remains largely underexplored. Herein, we report the intramolecular cyclopropanation of indoles with ene-yne ketones through zinc(II)/Co(III) furylcarbenes. A series of indolines bearing three-dimensional cyclic structures could be obtained with remarkable yields with high to very high diastereoselectivities.

Previous work



Scheme 1. Cyclopropane reactions of olefins and indoles with metal carbenes.

2. Experimental

2.1. General

All the chemicals were obtained from commercial sources and were used as-received unless otherwise noted. All the reactions were carried out under N₂ atmosphere using standard Schlenk technique. The ¹H NMR spectra were recorded on a 400-MHz or 600-MHz NMR spectrometer. The ¹³C NMR spectra were recorded at 100 MHz or 150 MHz. The ¹⁹F NMR spectra were recorded at 565 MHz. The chemical shifts were expressed in parts per million (δ) downfield from the internal standard tetramethylsilane and were reported as s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), m (multiplet), br s (broad singlet), etc. The residual solvent signals were used as references, and the chemical shifts were converted to the TMS scale. High resolution mass spectra were obtained on an Agilent Q-TOF 6540 spectrometer. Column chromatography was performed on silica gel (300–400 mesh) using ethyl acetate (EA)/petroleum ether (PE).

Substrate 1v was synthesized according to a literature report [56]; the others were prepared following published procedures [57–59]. Compounds **2a–2m** were prepared according to a literature report [47].

2.2. General procedure for synthesizing compounds 3

N-pyrimidinylindole (0.2 mmol), ene-yne ketones (0.24 mmol), [Cp*Co(MeCN)₃][SbF₆]₂ (5 mol%), and Zn(OAc)₂ (30 mol%) were charged into a Schlenk tube; anhydrous CH₂Cl₂ (2 mL) was added to this mixture under N₂ atmosphere. The reaction mixture was stirred at 45 °C for 12 h. After being cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography using PE/EA to obtain the product.

2.3. Spectral data for products

3aa was obtained according to the general procedure, with 94% yield, dr > 20:1; pale yellow solid. ¹H NMR (600 MHz, CDCl₃) δ 8.54 (d, *J* = 4.7 Hz, 2H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.34 (m, 2H), 7.29–7.21 (m, 3H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.78 (t, *J* = 4.7 Hz, 1H), 5.75 (s, 1H), 5.20 (d, *J* = 6.5 Hz, 1H), 3.51 (d, *J* = 6.5 Hz, 1H), 2.15 (s, 3H), 2.01 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 194.0, 159.8, 157.7, 147.8, 143.8, 142.0, 130.6, 128.7, 127.6, 126.7, 126.6, 124.8, 121.5, 121.3, 115.6, 112.7, 111.1, 51.9, 35.9, 28.8, 27.2, 14.0. HRMS calculated for C₂₆H₂₂N₃O₂⁺ (M + H)⁺: 408.1707; observed: 408.408.1709.

3ba was obtained according to the general procedure, with 62% yield, dr = 15:1; pale yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 8.54 (d, *J* = 4.8 Hz, 2H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.37–7.31 (m, 2H), 7.29–7.22 (m, 3H), 7.09 (t, *J* = 8.2 Hz, 1H), 6.78 (t, *J* = 4.8 Hz, 1H), 6.52 (d, *J* = 8.2 Hz, 1H), 5.80 (s, 1H), 5.14 (d, *J* = 6.6 Hz, 1H), 3.91 (s, 3H), 3.62 (d, *J* = 6.6 Hz, 1H), 2.17 (s, 3H), 2.04 (s, 3H). ¹³C NMR (151 MHz, CDCl₃) δ 194.0, 159.8, 157.7 (d, *J* = 7.4 Hz), 156.6, 148.1, 145.2, 142.1, 128.8, 128.6,

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