JYX JYVÄSKYLÄN YLIOPISTO UNIVERSITY OF JYVÄSKYLÄ

This is a self-archived version of an original article. This version may differ from the original in pagination and typographic details.

Author(s): Zhang, Jingyu; Xia, Wei; Qu, Meilin; Huda, Saskia; Ward, Jas; Rissanen, Kari; Albrecht, Markus

Title: Synthesis of Polycyclic Indolines utilizing a reduction/cyclization cascade reaction

Year: 2021

Version: Published version

Copyright: © 2021 The Authors. European Journal of Organic Chemistry published by Wiley-V

Rights: CC BY-NC-ND 4.0

Rights url: https://creativecommons.org/licenses/by-nc-nd/4.0/

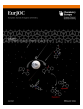
Please cite the original version:

Zhang, J., Xia, W., Qu, M., Huda, S., Ward, J., Rissanen, K., & Albrecht, M. (2021). Synthesis of Polycyclic Indolines utilizing a reduction/cyclization cascade reaction. European Journal of Organic Chemistry, 2021(45), 6097-6101. https://doi.org/10.1002/ejoc.202101191

EurJOC
European Journal of Organic Chemistry

Communications
doi.org/10.1002/ejoc.202101191

Chemistry Europe
European Chemical Societies Publishing



Synthesis of Polycyclic Indolines by Utilizing a Reduction/Cyclization Cascade Reaction

Jingyu Zhang,[a] Wei Xia,[a] Meilin Qu,[a] Saskia Huda,[a] Jas S. Ward,[b] Kari Rissanen,[b] and Markus Albrecht*[a]

In memory of Prof. Dr. Dieter Enders

Subsequent reduction and dearomatizing cyclization reactions open up an entry into the synthesis of novel N-fused polycyclic indolines. The dearomatizing cyclization as key step of the sequence proceeds well with $Cu(OTf)_2$ or TfOH as catalyst. At elevated temperature reduction of nitro-substituted precursors with iron under acidic conditions affords a broad variety of polycyclic indolines directly in a two-step cascade reaction in good to excellent yields. Using the developed protocol, the alkaloids tryptanthrin and phaitanthrin C have been prepared.

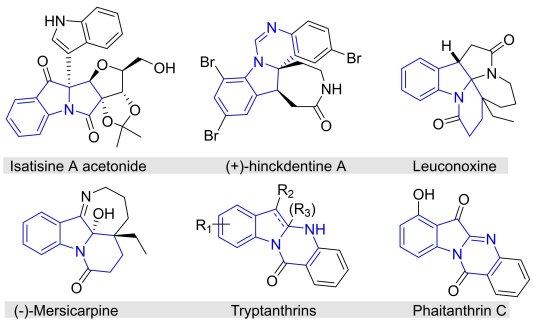
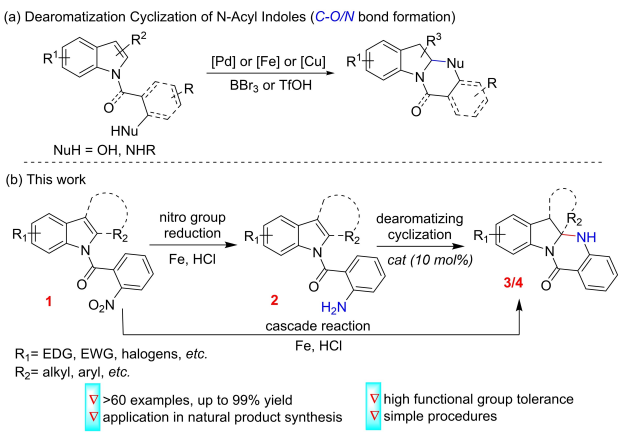


Figure 1. Natural products with N-fused polycyclic indolines.

Dearomatization reactions are recognized as a powerful tool to access diverse polycyclic scaffolds which are frequently encountered in alkaloid natural products and bioactives.[1] Aromatic feedstocks, owing to their widespread availability and ease of preparation, play an important role in synthetic organic chemistry.[2] Hereby, indole derivatives are well recognized in organic chemistry and their synthesis and functionalization have been intensely studied for over a century.[3] The dearomatization of indoles has been developed into one of the most attractive and straightforward approaches to access the indoline scaffold.[4] In past decades, numerous efforts have been made to perform effective dearomatization reactions, involving arylation, cycloaddition, oxidation, and others.[5] Various polycyclic indolines with a fused ring at C2, C3 positions have been prepared via this route as well (e.g., pyrroloindolines).[1c,d,4e,6]

Notably, novel polycyclic indolines with a fused ring at N1 and C2 positions are frequently found in alkaloid natural products and pharmaceuticals (Figure 1),[7] Some methods for the synthesis of the heterocyclic skeleton have been developed.[8] However, the increasing demand for novel and complex polycyclic indoline scaffolds has stimulated the search for general and efficient protocols.[9,10] To date, the dearomatizing cyclizations of N-substituted indoles to polycyclic indolines has been already developed.[11–14] E.g., dearomatization proceeds with C–C bond formation in the presence of Pd- or Ni-catalysts or by visible-light photocatalysis as well as others.[11] Recently, some approaches have been described, which involve C–O bond formation in the presence of Pd-catalysts, BBr_3 or triflic acid, and $FeCl_3$ (Scheme 1a).[12–14] To the best of our knowledge, N-acylindoles with amine or nitro groups as substrates are not systematically studied. Only one approach



Scheme 1. Dearomatization cyclization reactions of N-substituted indoles.

[a] J. Zhang, W. Xia, M. Qu, S. Huda, Prof. Dr. M. Albrecht
Institut für Organische Chemie
RWTH Aachen University
Landoltweg 1, Aachen 52074, Germany
E-mail: markus.albrecht@oc.rwth-aachen.de
https://www.albrecht.oc.rwth-aachen.de/go/id/jlfvy/?lidx=1
[b] Dr. J. S. Ward, Prof. Dr. K. Rissanen
University of Jyvaskyla, Department of Chemistry,
P.O. Box 35, Jyväskylä, Finland

Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202101191

© 2021 The Authors. European Journal of Organic Chemistry published by Wiley-VCH GmbH. This is an open access article under the terms of the Creative Commons Attribution Non-Commercial NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

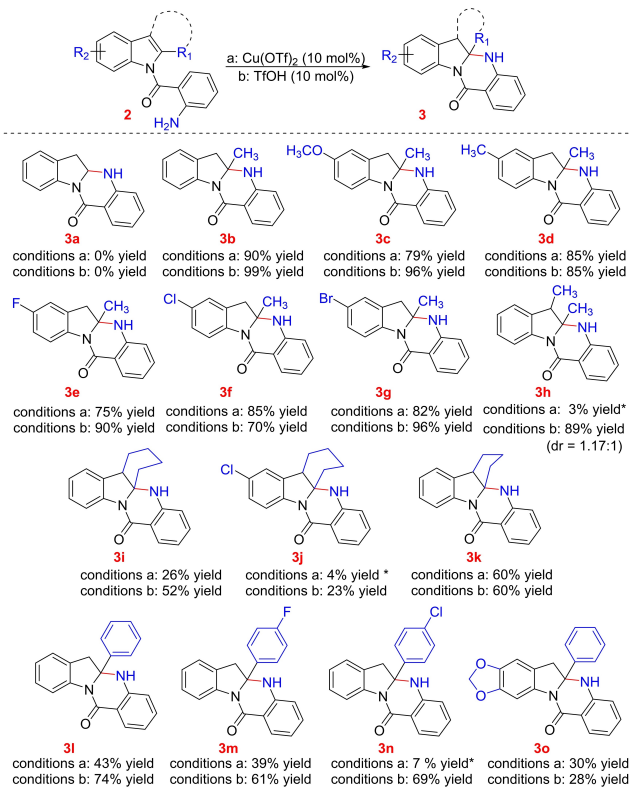
© 2021 The Authors. European Journal of Organic Chemistry published by Wiley-VCH GmbH

has been reported by us, in which the amine group was activated by a tosylate substituent (Scheme 1a).[14] Thus, it is desirable to develop simple and effective methods to access novel N-fused indolines.

Our recent research of the indole dearomatization reaction[13–14] catalyzed by $FeCl_3$[15] inspired us to expand the protocol to the direct synthesis of 5a,6-dihydroindolo[2,1-*b*]quinazolin-12(5*H*)-one as basic skeleton by intramolecular nucleophilic attack of an in situ generated non-activated NH_2-group to the C2-position of N-acyl indoles.[16]

Primary amines (as cyclization precursors) are easily available by reduction of nitro groups using iron metal in the presence of hydrochloric acid.[17] In order to study the synthesis of 5a,6-dihydroindolo[2,1-*b*]quinazolin-12(5*H*)-one derivatives **3**/**4** we started from nitrobenzoates **1** (Scheme 1b). Reduction of the nitrobenzoates **1** using Fe/HCl at room temperature affords the amines **2** which are required for the dearomatizing cyclization.

In a futile attempt we tried (2-aminophenyl)(1*H*-indol-1-yl) methanone (**2a**) in the dearomatizing cyclization with 10 mol% $Cu(OTf)_2$ (conditons a) or 10 mol% TfOH (conditions b) as catalysts (Scheme 2). $Cu(OTf)_2$ has been identified earlier as the superior catalyst for the analogous reaction with the corresponding activated tosyl amine.[14b] With the non-activated amine **2a** no reaction occurred. The nucleophilicity hereby is reduced by acidbinding, which does not take place in case of the analogous phenols. In addition, probably the electrophilicity of the C2 position of **2a** is not high enough. In order to establish higher electrophilicity at C2 a methyl group was installed in this position. Starting from **2b** the indoline **3b** was obtained in excellent yields under mild copper(II) triflate as well as TfOH catalysis. This cyclization is tolerating various kinds of substituents at the 6-membered ring of indole (e.g., CH_3, OCH_3, halogens (F, Cl, Br) at C5-position). Some variation of the substituent at 2-position is possible. However, it is required that the ("formal") positive charge at 2-position is stabilized.



Scheme 2. Synthesis of indolines via dearomatization reaction catalysed by $Cu(OTf)_2$ or TfOH. Reaction conditions a: **2** (0.2 mmol), $Cu(OTf)_2$ (10 mol%), $CHCl_3$ (0.1 mL), H_2O (20 µL), 60 °C, air, 48 h. Reaction conditions b: **2** (0.2 mmol), TfOH (10 mol%), $CHCl_3$ (0.1 mL), H_2O (20 µL), 60 °C, air, 48 h. * NMR yield.

The substrate with two methyl groups at C2- and C3-position results in 89% yield of **3h** with TfOH as catalyst but only 3% with $Cu(OTf)_2$. When C2- and C3-position are connected by an alkyl chain, moderate to good yields of cycloalkyl-fused indolines (**3i**–**3k**) are obtained. Moreover, aromatic substituents at C2-position, generally result in polycyclic indolines (**3l**–**3o**) in good yields. The observed results show that a higher stabilization of a positive charge at C2 of the indole results in higher yields. The yields in the presence of TfOH are generally higher than in the presence of $Cu(OTf)_2$ indicating that with the metal salt the generation of TfOH may produce the catalytically active species.[18]

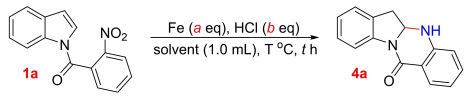
After establishing the amine cyclization it was desirable to obtain the dearomatized products in a simpler approach. When the iron powder/HCl reduction of the nitro compound **1a** was attempted at elevated temperature (boiling ethanol), the dearomatized product **3a**/**4a** was formed (49%). This transformation proceeds via a two-step cascade. Subsequently, optimization of different reaction parameters including the amount of iron and hydrochloric acid, the solvent, the reaction temperature, and the reaction time has been done (Table 1).

Under best conditions, product **4a** is obtained in 93% yield by treating **1a** with iron powder (5.0 eq.), hydrochloric acid (9.0 eq.) in 2-propanol (1.0 mL) at 90 °C for 18 hours under air. In addition, other metal powders have been tested with significantly reduced yields of **4a** (Al: 14%, Zn: 74%, Ni: 46%, Cu: 3%). For comparison reasons, $Cu(OTf)_2$ or TfOH were used as catalysts to cyclize **2a** in 2-propanol at 90 °C for 18 hours leading to **4a** in 25% or 87% yield, respectively. This yield is still lower compared to the two-step procedure shown in Table 1, entry 19.

With the optimized reaction conditions in hand, the substrate scope has been explored (Scheme 3). Indolines **3b**–**3p** with electron donating groups in 2-position of the indole skeleton[19] are obtained in excellent yields of 79–99% (Scheme 3). The yields of the two step procedure are much higher than the ones obtained with $Cu(OTf)_2$ or HOTf for only the cyclization step. In addition, the indolines **4a**–**4p** can be obtained from the corresponding N-acylindoles without activation of the 2-position of indole by substituents. However, the yields drop to, e.g., 15% in case of **4h** with an electron withdrawing group in 5-position destabilizing a cation in 2-position. Some X-ray structures (2080687 (for **3c**), 2080688 (for **3e**), 2080689 (for **3f**), 2080690 (for **3h**), 2080691 (for **3n**)) have been obtained from indoline derivatives, which nicely show the

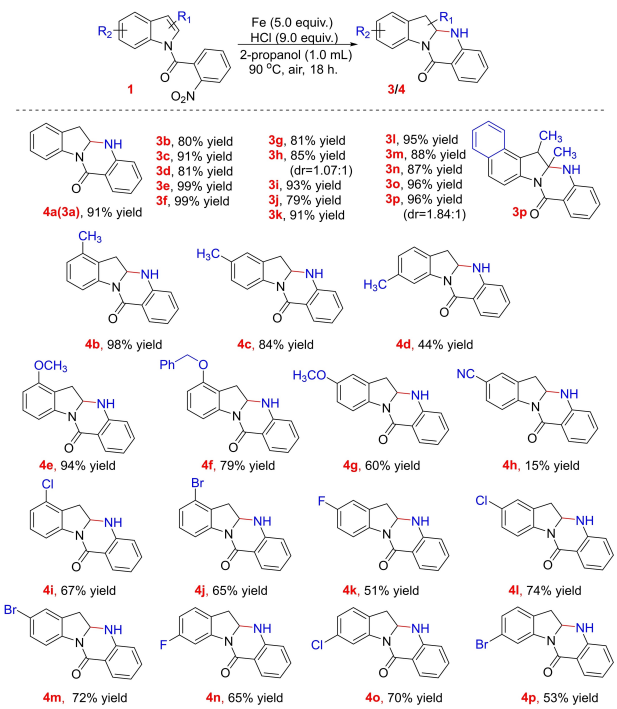
© 2021 The Authors. European Journal of Organic Chemistry published by Wiley-VCH GmbH

Table 1. Optimization of the two-step cascade reaction of **1a** to obtain **4a**.[a]



Entry	Fe [eq.]	HCl [eq.]	Solvent	T [°C]	*t* [h]	**4a** [%][b]
1	5	12	EtOH	80	6	49
2	5	9	EtOH	80	6	54
3	5	6	EtOH	80	6	46
4	5	3	EtOH	80	6	6
5	7	9	EtOH	80	6	45
6	4	9	EtOH	80	6	44
7	3	9	EtOH	80	6	0
8	5	9	EtOH	80	12	65
9	5	9	EtOH	80	18	73
10	5	9	EtOH	80	24	70
11	5	9	EtOH	70	18	42
12	5	9	EtOH	90	18	77
13	5	9	EtOH	100	18	67
14	5	9	toluene	90	18	0
15	5	9	CH_3CN	90	18	69
16	5	9	CH_3NO_2	90	18	0
17	5	9	DMF	90	18	5
18	5	9	DMSO	90	18	22
19	5	9	2-propanol	90	18	93 (91)
20	5	9	1-propanol	90	18	60
21	5	9	1-butanol	90	18	76

[a] Unless otherwise noted, all reactions were performed on a 0.2 mmol scale, with 1.0 mL of solvent in a sealed tube under air. [b] Yields were determined by ^{1}H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; the yield given in brackets corresponds to the isolated yield.



Scheme 3. Substrate scope for the reduction/cyclization sequence. Reaction conditions: **1** (0.2 mmol), Fe (5.0 equiv.), HCl (9.0 equiv.) in 2-propanol (1.0 mL) at 90 °C for 18 h.

slightly bent shape of the tetracyclic dearomatized indoline based moieties (Figure 2).

Nevertheless, it has to be mentioned that some derivatives (**5a–g**) cannot be obtained via the described route. This is due to destabilization of the required cation stabilization in 2-position of the precursor (**5a–e**) or by steric effects between the N-acyl unit with the substituent in 7-position of the indole (**5f**). **5g** probably is not obtained due to conformational restrictions at the SO_2-unit (Figure 3).

From a mechanistic point of view, the cascade reaction is an acid catalysed process. Initiated by the reduction of the nitro group of **1** the amine **2** is formed which is activated by addition of acids to the 3-position of the indole as well as to the carbonyl of the acyl moiety. This enables attack of the amine to the 2-position of indole to finally obtain compounds **3**/**4** (Scheme 4). Hereby, it cannot be decided if iron salt or HCl is the active catalyst. Control experiments show that under standard reaction conditions HCl as well as iron(II) chloride are able to catalyse the cyclization of the amine **2a** to the indolines **3a**/**4a** in low yields (45% or 14%, respectively). This may indicate a cooperative effect between the Bronsted and the Lewis-acid.

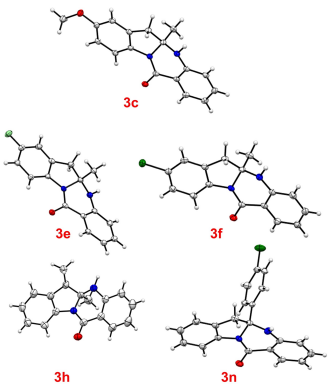


Figure 2. Molecular structures of **3c**, **3e**, **3f**, **3h**, **3n**. Deposition Numbers 2080687 (for **3c**), 2080688 (for **3e**), 2080689 (for **3f**), 2080690 (for **3h**), 2080691 (for **3n**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

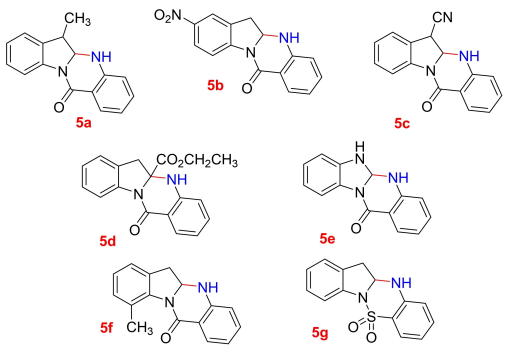
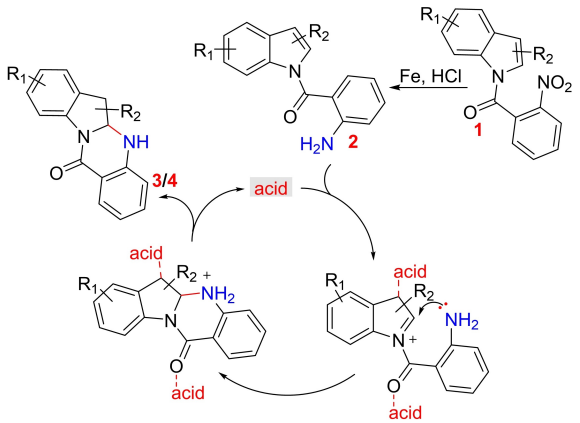


Figure 3. Indolines which cannot be obtained by methods presented in here.

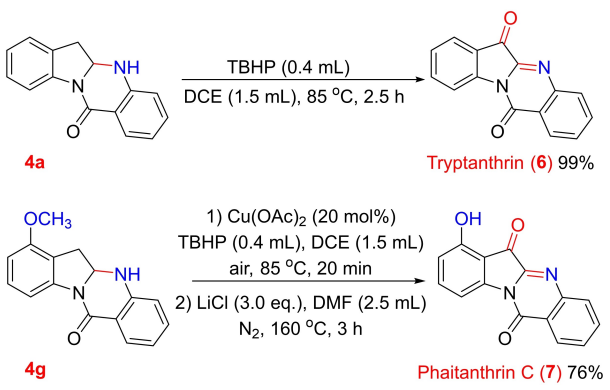
© 2021 The Authors. European Journal of Organic Chemistry published by Wiley-VCH GmbH



Scheme 4. Proposed mechanism for the formation of the indolines **3** or **4**.

Thus, in here a versatile protocol for the one-pot two-step preparation of tetracyclic indolines from simple nitro substituted N-benzoates of indole is presented. In order to show the value of the described procedure selected cyclization products have been applied to obtain alkaloids (Scheme 5). Oxidation of **4a** proceeds smoothly by reaction with *t*-butyl hydroperoxide and affords the naturally occurring alkaloid tryptanthrin in quantitative yield with an overall yield of 90% starting from **1a**. Phaitanthrin C is obtained from the cyclization product **4g** by oxidation followed by cleavage of the methyl ether in 76% yield.

In conclusion, we developed versatile protocols for the synthesis of diverse novel N-fused polycyclic indolines. $Cu(OTf)_2$ and TfOH are mild catalysts for the intramolecular dearomatizing amination of N-acylindoles. Based on this, a concise one-pot nitro reduction/dearomatization cascade reaction is developed in here. Simple experimental protocols, cheap and widespread availability of the starting materials, wide range tolerance of functional groups, and good to excellent yields make this procedure attractive for the preparation of polycyclic indolines. Based on our preliminary studies, we expect that these protocols will be further applied to the synthesis of alkaloid natural products and bioactives.



Scheme 5. Preparation of alkaloids tryptanthrin as well as phytanthrin C from polycyclic indolines **4a** or **4g**.

Acknowledgements

J.Z. gratefully acknowledges support by the Chinese Scholarship Council (CSC). K.R. acknowledges an award by the Alexander von Humbold foundation. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Acid catalysis · Cyclization · Cascade reactions · Dearomatization · Nitrogen heterocycles

[1] a) F. L. Ortiz, M. J. Iglesias, I. Fernández, C. M. A. Sánchez, G. R. Gómez, *Chem. Rev.* **2007**, *107*, 1580–1691; b) A. R. Pape, K. P. Kaliappan, E. P. Kündig, *Chem. Rev.* **2000**, *100*, 2917–2940; c) S. P. Roche, J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068–4093; *Angew. Chem.* **2011**, *123*, 4154–4179; d) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662–12686; *Angew. Chem.* **2012**, *124*, 12834–12858; e) C.-X. Zhuo, C. Zheng, S.-L. You, *Acc. Chem. Res.* **2014**, *47*, 2558–2573.

[2] a) C. Zheng, S.-L. You, *Chem* **2016**, *1*, 830–857; b) W. C. Wertjes, E. H. Southgate, D. Sarlah, *Chem. Soc. Rev.* **2018**, *47*, 7996–8017; c) C. J. Huck, D. Sarlah, *Chem* **2020**, *6*, 1589–1603.

[3] For selected reviews, see: a) G. Bartoli, G. Bencivenni, R. Dalpozzo, *Chem. Soc. Rev.* **2010**, *39*, 4449–4465; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2011**, *111*, PR215-PR283; c) R. Dalpozzo, *Chem. Soc. Rev.* **2015**, *44*, 742–778; d) A. A. Festa, L. G. Voskressensky, E. V. Van der Eycken, *Chem. Soc. Rev.* **2019**, *48*, 4401–4423; e) T. Guo, F. Huang, L. Yu, Z. Yu, *Tetrahedron Lett.* **2015**, *56*, 296–302; f) L. S. Hegedus, *Angew. Chem. Int. Ed.* **1988**, *27*, 1113–1126; *Angew. Chem.* **1988**, *100*, 1147–1161; g) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911; h) S. Liu, F. Zhao, X. Chen, G.-J. Deng, H. Huang, *Adv. Synth. Catal.* **2020**, *362*, 3795–3823; i) X.-Y. Liu, Y. Qin, *Acc. Chem. Res.* **2019**, *52*, 1877–1891; j) K. Nagaraju, D. Ma, *Chem. Soc. Rev.* **2018**, *47*, 8018–8029; k) M. Platon, R. Amardeil, L. Djakovitch, J.-C. Hierso, *Chem. Soc. Rev.* **2012**, *41*, 3929–3968; l) E. Stempel, T. Gaich, *Acc. Chem. Res.* **2016**, *49*, 2390–2402; m) D. F. Taber, P. K. Tirunahari, *Tetrahedron* **2011**, *67*, 7195–7210; n) L. Zheng, K. Tao, W. Guo, *Adv. Synth. Catal.* **2021**, *363*, 62–119.

[4] For selected reviews, see: a) J. Bariwal, L. G. Voskressensky, E. V. Van der Eycken, *Chem. Soc. Rev.* **2018**, *47*, 3831–3848; b) H. Abou-Hamdan, C. Kouklovsky, G. Vincent, *Synlett* **2020**, *31*, 1775–1788; c) Q. Ding, X. Zhou, R. Fan, *Org. Biomol. Chem.* **2014**, *12*, 4807–4815; d) M. J. James, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J.* **2016**, *22*, 2856–2881; e) S. P. Roche, J.-J. Youte Tendoung, B. Tréguier, *Tetrahedron* **2015**, *71*, 3549–3591; f) W. Zi, Z. Zuo, D. Ma, *Acc. Chem. Res.* **2015**, *48*, 702–711.

[5] For selected examples of dearomatization reaction, see a) N. T. Vo, R. D. M. Pace, F. O'Hara, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 404–405; b) B. M. Trost, J. Quancard, *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315; c) S. Rousseaux, J. García-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 9282–9285; d) K.-J. Wu, L.-X. Dai, S.-L. You, *Org. Lett.* **2012**, *14*, 3772–3775; e) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804–16805; f) G. Zhang, X. Huang, G. Li, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 1814–1815; g) Q.-F. Wu, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 1680–1683; *Angew. Chem.* **2012**, *124*, 1712–1715; h) F. J. Robertson, B. D. Kenimer, J. Wu, *Tetrahedron* **2011**, *67*, 4327–4332; i) M. Kawano, T. Kiuchi, S. Negishi, H. Tanaka, T. Hoshikawa, J. Matsuo, H. Ishibashi, *Angew. Chem. Int. Ed.* **2013**, *52*, 906–910; *Angew. Chem.* **2013**, *125*, 940–944; j) A. Lin, J. Yang, M. Hashim, *Org. Lett.* **2013**, *15*, 1950–1953; k) J. Gagnepain, F. Castet, S. Quideau, *Angew. Chem. Int. Ed.* **2007**, *46*, 1533–1535; *Angew. Chem.* **2007**, *119*,

© 2021 The Authors. European Journal of Organic Chemistry published by Wiley-VCH GmbH

1555–1557; l) N. Kagawa, J. P. Malerich, V. H. Rawal, *Org. Lett.* **2008**, *10*, 2381–2384; m) L. M. Repka, J. Ni, S. E. Reisman, *J. Am. Chem. Soc.* **2010**, *132*, 14418–14420; n) L.-Y. Mei, Y. Wei, X.-Y. Tang, M. Shi, *J. Am. Chem. Soc.* **2015**, *137*, 8131–8137; o) D. B. C. Martin, C. D. Vanderwal, *J. Am. Chem. Soc.* **2009**, *131*, 3472–3473; p) E. H. Southgate, J. Pospech, J. Fu, D. R. Holycross, D. Sarlah, *Nat. Chem.* **2016**, *8*, 922–928.

[6] For selected reviews, see: a) L. M. Repka, S. E. Reisman, *J. Org. Chem.* **2013**, *78*, 12314–12320; b) G. Huang, B. Yin, *Adv. Synth. Catal.* **2019**, *361*, 405–425.

[7] a) A. Umehara, H. Ueda, H. Tokuyama, *Org. Lett.* **2014**, *16*, 2526–2529; b) R. Nakajima, T. Ogino, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2010**, *132*, 1236–1237; c) S. Yang, X. Li, F. Hu, Y. Li, Y. Yang, J. Yan, C. Kuang, Q. Yang, *J. Med. Chem.* **2013**, *56*, 8321–8331; d) Z. Xu, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2013**, *135*, 19127–19130; e) J.-F. Liu, Z.-Y. Jiang, R.-R. Wang, Y.-T. Zheng, J.-J. Chen, X.-M. Zhang, Y.-B. Ma, *Org. Lett.* **2007**, *9*, 4127–4129; f) K. Higuchi, Y. Sato, M. Tsuchimochi, K. Sugiura, M. Hatori, T. Kawasaki, *Org. Lett.* **2009**, *11*, 197–199; g) K. Douki, H. Ono, T. Taniguchi, J. Shimokawa, M. Kitamura, T. Fukuyama, *J. Am. Chem. Soc.* **2016**, *138*, 14578–14581; h) J. Lee, J. S. Panek, *Org. Lett.* **2011**, *13*, 502–505; i) C.-W. Jao, W.-C. Lin, Y.-T. Wu, P.-L. Wu, *J. Nat. Prod.* **2008**, *71*, 1275–1279.

[8] a) S. J. Mahoney, E. Fillion, *Chem. Eur. J.* **2012**, *18*, 68–71; b) Z. Zhang, D. Yi, M. Zhang, J. Wei, J. Lu, L. Yang, J. Wang, N. Hao, X. Pan, S. Zhang, S. Wei, Q. Fu, *ACS Catal.* **2020**, *10*, 10149–10156; c) S. J. Gharpure, Y. G. Shelke, D. P. Kumar, *Org. Lett.* **2015**, *17*, 1926–1929; d) N. Arai, T. Ohkuma, *Org. Lett.* **2019**, *21*, 1506–1510; e) S. J. Gharpure, Y. G. Shelke, *Org. Lett.* **2017**, *19*, 5022–5025.

[9] C. J. O′ Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 4444–4456.

[10] a) A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons, D. W. Young, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6799–6804; b) K. C. Morrison, P. J. Hergenrother, *Nat. Prod. Rep.* **2014**, *31*, 6–14.

[11] a) J.-J. Wang, A.-X. Zhou, G.-W. Wang, S.-D. Yang, *Adv. Synth. Catal.* **2014**, *356*, 3356–3362; b) J. Wang, Y. Liu, Z. Xiong, L. Zhong, S. Ding, L. Li, H. Zhao, C. Chen, Y. Shang, *Chem. Commun.* **2020**, *56*, 3249–3252; c) C. Shen, R.-R. Liu, R.-J. Fan, Y.-L. Li, T.-F. Xu, J.-R. Gao, Y.-X. Jia, *J. Am. Chem. Soc.* **2015**, *137*, 4936–4939; d) W.-J. Zhou, Z.-H. Wang, L.-L. Liao, Y.-X. Jiang, K.-G. Cao, T. Ju, Y. Li, G.-M. Cao, D.-G. Yu, *Nat. Commun.* **2020**, *11*, 3263; e) L. Zhao, Z. Li, L. Chang, J. Xu, H. Yao, X. Wu, *Org. Lett.* **2012**, *14*, 2066–2069; f) N. Zeidan, T. Beisel, R. Ross, M. Lautens, *Org. Lett.* **2018**, *20*, 7332–7335; g) D. A. Petrone, A. Yen, N. Zeidan, M. Lautens, *Org. Lett.* **2015**, *17*, 4838–4841; h) X. Li, B. Zhou, R.-Z. Yang, F.-M. Yang, R.-X. Liang, R.-R. Liu, Y.-X. Jia, *J. Am. Chem. Soc.* **2018**, *140*, 13945–13951; i) M.-L. Han, W. Huang, Y.-W. Liu, M. Liu, H. Xu, H. Xiong, H.-X. Dai, *Org. Lett.* **2021**, *23*, 172–177; j) S. R. Flanagan, D. C. Harrowven, M. Bradley, *Tetrahedron Lett.* **2003**, *44*, 1795–1798; k) D. A. Petrone, M. Kondo, N. Zeidan, M. Lautens, *Chem. Eur. J.* **2016**, *22*, 5684–5691; l) A. D. Marchese, F. Lind, Á. E. Mahon, H. Yoon, M. Lautens, *Angew. Chem. Int. Ed.* **2019**, *58*, 5095–5099; *Angew. Chem.* **2019**, *131*, 5149–5153; m) R.-R. Liu, Y.-G. Wang, Y.-L. Li, B.-B. Huang, R.-X. Liang, Y.-X. Jia, *Angew. Chem. Int. Ed.* **2017**, *56*, 7475–7478; *Angew. Chem.* **2017**, *129*, 7583–7586; n) X. Qin, M. W. Y. Lee, J. S. Zhou, *Angew. Chem. Int. Ed.* **2017**, *56*, 12723–12726; *Angew. Chem.* **2017**, *129*, 12897–12900; o) C. Shen, N. Zeidan, Q. Wu, C. B. J. Breuers, R.-R. Liu, Y.-X. Jia, M. Lautens, *Chem. Sci.* **2019**, *10*, 3118–3122; p) H. Wang, X.-F. Wu, *Org. Lett.* **2019**, *21*, 5264–5268.

[12] a) O. Lozano, G. Blessley, T. Martinez Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.* **2011**, *50*, 8105–8109; *Angew. Chem.* **2011**, *123*, 8255–8259; b) X. Fang, S. Gao, Z. Wu, H. Yao, A. Lin, *Org. Chem. Front.* **2017**, *4*, 292–296.

[13] J. M. Hartmann, M. de Groot, K. Schäringer, K. Henke, K. Rissanen, M. Albrecht, *Eur. J. Org. Chem.* **2018**, *2018*, 901–907.

[14] a) J. Zhang, J. Li, J. S. Ward, K.-N. Truong, K. Rissanen, M. Albrecht, *J. Org. Chem.* **2020**, *85*, 12160–12174; b) J. Zhang, W. Xia, S. Huda, J. S. Ward, K. Rissanen, M. Albrecht, *Adv. Synth. Catal.* **2021**, *363*, 3121–3126.

[15] For selected reviews, see: a) I. Bauer, H.-J. Knölker, *Chem. Rev.* **2015**, *115*, 3170–3387; b) S. Rana, J. P. Biswas, S. Paul, A. Paik, D. Maiti, *Chem. Soc. Rev.* **2021**, *50*, 243–472.

[16] For other dearomatizing reactions at indole see: a) B. Han, Y.-C. Xiao, Y. Yao, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 10189–10191; *Angew. Chem.* **2010**, *122*, 10387–10389; b) F. Nowrouzi, R. A. Batey, *Angew. Chem. Int. Ed.* **2013**, *52*, 892–895; *Angew. Chem.* **2013**, *125*, 926–929; c) Y. N. Bubnov, I. V. Zhun′, E. V. Klimkina, A. V. Ignatenko, Z. A. Starikova, *Eur. J. Org. Chem.* **2000**, *2000*, 3323–3327; d) R. Alam, C. Diner, S. Jonker, L. Eriksson, K. J. Szabó, *Angew. Chem. Int. Ed.* **2016**, *55*, 14417–14421; *Angew. Chem.* **2016**, *128*, 14629–14633; e) R. Beaud, R. K. Nandi, A. Perez-Luna, R. Guillot, D. Gori, C. Kouklovsky, N.-E. Ghermani, V. Gandon, G. Vincent, *Chem. Commun.* **2017**, *53*, 5834–5837.

[17] a) S. K. Sharma, A. K. Mandadapu, K. Kumaresan, A. Arora, H. M. Gauniyal, B. Kundu, *Synthesis* **2010**, 4087–4095; b) L. Wang, S. Xie, L. Ma, Y. Chen, W. Lu, *Bioorg. Med. Chem.* **2015**, *23*, 1950–1962; c) Y. Liu, Y. Lu, M. Prashad, O. Repič, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*, 217–219; d) S. Butini, E. Gabellieri, P. B. Huleatt, G. Campiani, S. Franceschini, M. Brindisi, S. Ros, S. S. Coccone, I. Fiorini, E. Novellino, G. Giorgi, S. Gemma, *J. Org. Chem.* **2008**, *73*, 8458–8468; e) U. Galli, C. Travelli, S. Aprile, E. Arrigoni, S. Torretta, G. Grosa, A. Massarotti, G. Sorba, P. L. Canonico, A. A. Genazzani, G. C. Tron, *J. Med. Chem.* **2015**, *58*, 1345–1357.

[18] M. J.-L. Tschan, C. M. Thomas, H. Strub, J.-F. Carpentier, *Adv. Synth. Catal.* **2009**, *351*, 2496–2504.

[19] For the problem to generate quaternary centers in natural product synthesis see: P. Hu, H. M. Chi, K. C. DeBacker, X. Gong, J. H. Keim, I. T. Hsu, S. A. Snyder, *Nature* **2019**, *569*, 703–707.

Manuscript received: September 23, 2021
Revised manuscript received: October 4, 2021
Accepted manuscript online: October 7, 2021

© 2021 The Authors. European Journal of Organic Chemistry published by Wiley-VCH GmbH