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Dearomatization of electron poor six-membered N-heterocycles through [3 + 2] annulation with aminocyclopropanes†

Johannes Preindl, Shyamal Chakrabarty‡ and Jérôme Waser *

Many abundant and highly bioactive natural alkaloids contain an indolizidine skeleton. A simple, high yielding method to synthesize this scaffold from N-heterocycles was developed. A wide range of pyridines, quinolines and isoquinolines reacted with donor–acceptor (DA)-aminocyclopropanes *via* an ytterbium(III) catalyzed [3 + 2] annulation reaction to give tetrahydroindolizidine derivatives. The products were obtained with high diastereoselectivities (*dr* > 20 : 1) as *anti*-isomers. Additionally, the formed amins could be easily converted into secondary and tertiary amines through iminium formation followed by reduction or nucleophile addition. This transformation constitutes the first example of dearomatization of electron-poor six-membered heterocycles *via* [3 + 2] annulation with DA cyclopropanes.

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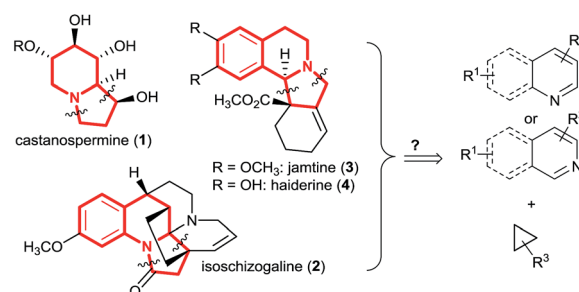
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1. Introduction

The indolizidine skeleton is widely represented in bioactive alkaloids.¹ For example, castanospermine (**1**, Scheme 1) is a potent inhibitor of α -glucosidase I, an enzyme with a critical role in viral maturation, and was the lead structure for celgosivir which is currently under investigation for treatment of hepatitis C virus infection and dengue fever.² The indolizidine class of natural products also includes more complex polycyclic compounds incorporating further fused saturated or unsaturated rings.³ For instance, isoschizogaline (**2**) contains a reduced quinoline core structure,^{3a} whereas jamine (**3**)^{3b} or haiderine (**4**)^{3c} can be seen as isoquinoline derived alkaloids. The construction of these polycyclic scaffolds by dearomatization of quinolines, isoquinolines or pyridines is highly attractive, due to the broad availability of the unsaturated heterocycles. Classic dearomatization strategies most often rely on the formation of a single bond, starting from activated pyridinium or (iso)quinolinium intermediates.⁴ Dearomatization reactions through direct annulation *via* ring-extension of

cyclopropanes would provide a more convergent synthesis (Scheme 1). Nevertheless, such processes are unknown.⁵

In this context, Lewis acid (LA) catalyzed [3 + 2] annulation reactions of donor–acceptor (DA) cyclopropanes with dipolarophiles have been intensively studied.⁶ In particular, these reactions are highly successful with enol-ethers,⁷ nitrosoarenes,⁸ imines,⁹ heteroatom substituted alkynes,¹⁰ carbonyl compounds¹¹ and nitrones.¹² However, dearomative [3 + 2] annulation reactions were only intensively studied with indoles¹³ and a single example was reported for benzothiazoles (Scheme 2).¹⁴ Therefore, only [6,5,5] polycyclic ring systems can be currently accessed, although this approach would appear highly attractive for the synthesis of other polycyclic scaffolds as well. In fact, indole, with its high nucleophilicity and low aromatization energy (28 kcal mol⁻¹ only for the pyrrole ring),¹⁵ constitutes an ideal case for dearomatization reactions: the nucleophilic character leads to a fast reaction with Lewis acid activated DA cyclopropanes, and the lower aromatization energy makes isolation of the saturated products easier.



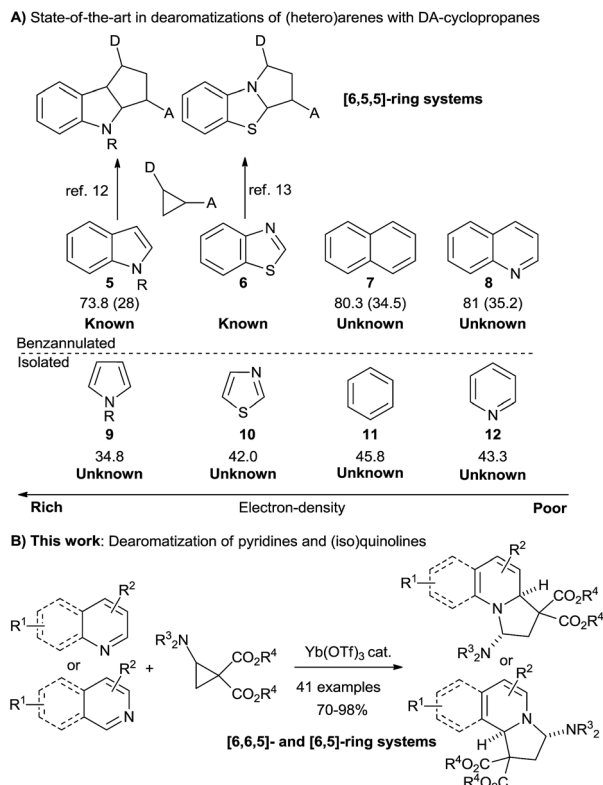
Scheme 1 Examples for indolizidine containing natural products and general retrosynthetic scheme.

Laboratory of Catalysis and Organic Synthesis, Institut des Sciences et Ingénierie Chimiques, École Polytechnique Fédérale de Lausanne, CH-1015 Lausanne, Switzerland. E-mail: jerome.waser@epfl.ch

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‡ Dr Chakrabarty has decided to stop his scientific career and cannot be contacted any more. He therefore did not see the final version of this manuscript. Based on his important contribution to the project, both J. P. and J. W. agree to include him as co-author and are convinced that he would agree to be included if he knew about this submission.





Scheme 2 Dearomatization via [3 + 2] annulations with DA-cyclopropanes.

Dearomatizing electron-poor quinolines with higher aromatization energy (35 kcal mol⁻¹ for the pyridine ring) is much more challenging. In 2006, Pagenkopf and coworkers reported a method for the formation of indolizines *via* [3 + 2] annulation of pyridines or quinolines with DA cyclopropanes.^{16a} In this work, dihydroindolizines were observed as intermediates, but they could be only isolated in very low yield and partially oxidized to indolizines. Therefore, the authors decided to completely aromatize the crude product with manganese(IV) oxide to obtain single, clean products. Later, Wang and coworkers used a similar approach with iodine as oxidant for indolizine synthesis.^{16b}

Compared to bicyclic aromatic compounds, the dearomatization of monocyclic aromatics is even more challenging due to increased resonance stabilization. It is therefore not surprising that no dearomatizing [3 + 2] annulation was yet reported for these compounds.

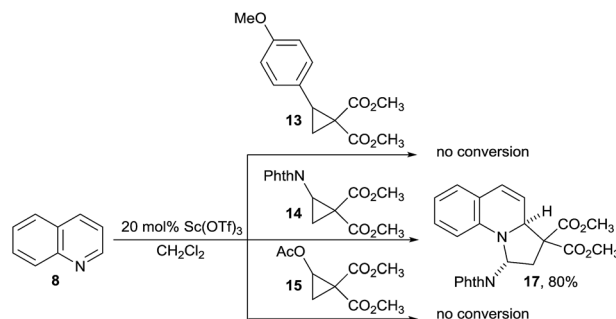
Herein we describe the dearomative [3 + 2] annulation of N-heterocycles with aminocyclopropanes to generate tetrahydroindolizines with high yield and stereoselectivity. Key for success were the exceptional properties of imido-substituted DA diester cyclopropanes, as other types of donor groups were not successful. A broad substrate scope including pyridines, quinolines, and isoquinolines is presented. The obtained amins can be easily modified through iminium formation and subsequent reduction or nucleophile addition.

2. Results and discussion

2.1. Preliminary results and optimization

We started our investigations by examining the reactions of DA acceptor cyclopropanes with quinoline (**8**) using scandium triflate as a Lewis acid catalyst (Scheme 3). Under these conditions, no reactivity was observed using well-established aryl-substituted DA cyclopropane **13**.⁶ We then wondered if DA cyclopropanes bearing a heteroatom donor group would be more reactive.^{7c} Indeed, cyclopropane **14** bearing a phthalimide donor led to the formation of [3 + 2] annulation product **17** in 80% yield. Cyclopropane **14** is easily available in one step on multigram scale from *N*-vinylphthalimide and diazomalones by Rh-catalyzed cyclopropanation.¹⁷ In contrast, no conversion was observed with cyclopropane **15** bearing an oxygen donating group. This results further highlight the unique reactivity of imido-substituted DA cyclopropanes. Gratifyingly, compound **17** was stable enough to be isolated and fully characterized. The *cis*-relationship of the phthalimide and the hydrogen at ring junction was confirmed by X-ray analysis (Fig. 1).¹⁸

We then turned to the optimization of the [3 + 2] annulation. Product **17** was formed with >20 : 1 *anti* diastereoselectivity and 80% yield using Sc(OTf)₃ as catalyst (Table 1, entry 1). Nevertheless, this result could only be obtained with 1.5 equiv. of cyclopropane **14** and relatively low molarity (0.05 M) to prevent decomposition. Furthermore, the amount of Sc(OTf)₃ could not be reduced. Therefore, other Lewis acids were examined. No reaction was observed with In(OTf)₃ or Cu(OTf)₂ as catalysts (Table 1, entries 2 and 3) whereas the use of Hf(OTf)₄ resulted in full decomposition of the DA-cyclopropane **14** (Table 1, entry 4). Better results were obtained using Yb(OTf)₃ as catalyst. A first experiment gave 90% of the desired product **17** while the high diastereoselectivity was maintained (Table 1, entry 5). Furthermore, the mild conditions with Yb(OTf)₃ allowed us to conduct the reaction more concentrated (0.5 M), with only 1.05 equivalents **14** and at lower catalyst loading (5 mol%) without observing any decrease in yield (Table 1, entry 6).¹⁹ The reaction proved to be easily scalable, as the yield did not change on 2 mmol scale. Eventual Brønsted acid catalysis of the reaction could be excluded by a control experiment with triflic acid (Table 1, entry 7). No reaction between **8** and *para*-methoxy phenyl or acetate substituted DA cyclopropanes (**13** and **15**) was again observed in presence of catalytic amounts of ytterbium(III) triflate (Table 1, entries 8 and 9).



Scheme 3 Preliminary results on the dearomatization of quinoline (**8**).



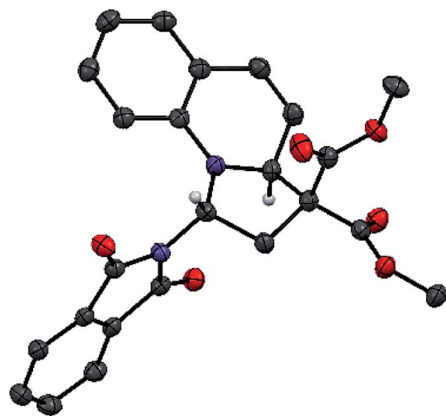


Fig. 1 Structure of compound 17 as determined by X-ray analysis. Some hydrogen atoms are omitted for clarity.

2.2. Scope of the [3 + 2] annulation

Next, the scope of the reaction was examined by submitting various quinolines to the optimized reaction conditions (Fig. 2). Substitution of the pyridine ring was examined first (Fig. 2A). Alkyl, alkynyl and halogen substituents were all well tolerated either in C3 or C4 position of the quinoline ring (products 20–25). To our delight, *O*-acetylated cinchonidine with its highly basic amine worked well and furnished compound 22 in 76% yield and 1 : 1 dr. A broad range of versatile substituents such as aryl, halogens, trifluoromethyl, ester, nitrile and nitro were also tolerated on the arene ring (Fig. 2B, products 26–34). Generally, no differences in term of reactivity were observed upon substitution of the benzene or the pyridine ring of the employed quinolines. Only 2- and 8-substituted quinolines did not react

under the developed conditions (with the exception of the fluoro substituent, product 31), probably due to increased steric hindrance. As a limitation, dearomatization of highly electron-rich 6-methoxy quinoline was not successful and compound 33 could not be obtained. Overall, the tolerance of functional groups attached to the quinoline is extremely broad, including in particular:

- Potentially sensitive π -systems, such as alkenes and alkynes (products 22, 24 and 25).
- Strongly electron-withdrawing groups, such as esters, cyano and nitro, which are useful precursors of amides or amines (products 29, 30 and 34).
- Halogens, which are easily further modified using cross-coupling chemistry (products 20 and 26) or useful to diminish the electron-density of the heterocycle for pharmaceutical or agrochemical purposes (especially fluorine, products 27 and 31)
- Highly basic tertiary amines (product 22).

The influence of different nitrogen substituents on the DA-cyclopropane was then investigated (Fig. 2C). Less electron donating phthalimide groups with chloro or nitro substituents gave the desired products 35 and 36 in good yields, but their stability was significantly lower compared to their unsubstituted relative 17. Furthermore, maleimide, succinimide or a 2,3-naphthimide substituted DA cyclopropanes could also be used under the developed conditions (products 37–39). Finally, different ester groups on the cyclopropane had low impact on the reaction outcome (Fig. 2D): replacing the methyl esters of 14 with benzyl or trifluoroethyl esters gave the desired products 40 and 41 in excellent yields. With a mixed diester, product 42 was isolated in 72% yield, and 3.5 : 1 dr at the additional stereogenic center.

At this point we wondered if the developed protocol for the dearomatization of quinoline could also be applied to other N-heterocycles. To our delight isoquinoline reacted equally well and furnished 43 with 83% yield and high diastereoselectivity (>20 : 1, Fig. 3A). Cyano and ester substituted isoquinolines reacted also well under the developed conditions (products 44 and 45). The scope of the reaction could be extended to benzothiazole and benzoxazole (Fig. 3B, products 46 and 47).

Further expansion of the scope to pyridines proved to be more difficult. Unsubstituted pyridines or pyridines with electron donating substituents did not react to form the desired products under the developed conditions. It is known, that nucleophilic ring opening of acceptor substituted cyclopropanes with pyridine furnishes betaine products.²⁹ Ring closure was expected to be more favored with electron deficient pyridines, as the positive charge of the betaine intermediate is then less stabilized. Indeed, the desired dearomative [3 + 2] annulation products of electron-deficient pyridines and 6a were isolated with good yield and high diastereoselectivity (>20 : 1) when the catalyst loading was raised to 10 mol% and the concentration to 1 M (Fig. 3C). Nicotinonitrile as well as isonicotinonitrile gave the desired products 48 and 49 with high yield. 4-Methyl, bromo-, or alkyl-substituted nicotinonitrile could also be used (products 50–52). Remarkably, the annulation reaction was completely regioselective for the less sterically hindered position. Such a high selectivity has been only rarely

Table 1 Optimization of the dearomative [3 + 2] annulation reaction of quinoline 8 and DA cyclopropanes 13–15^a

| Entry | R | LA | Mol% | Yield ^b |
|----------------|-------|----------------------|------|----------------------|
| 1 | NPhth | Sc(OTf) ₃ | 20 | 80 |
| 2 | NPhth | In(OTf) ₃ | 20 | No conversion |
| 3 | NPhth | Cu(OTf) ₂ | 20 | No conversion |
| 4 | NPhth | Hf(OTf) ₄ | 20 | Decomposition |
| 5 | NPhth | Yb(OTf) ₃ | 20 | 90 |
| 6 ^c | NPhth | Yb(OTf) ₃ | 5 | 96 (95) ^d |
| 7 ^e | NPhth | TfOH | 20 | No conversion |
| 8 | PMP | Yb(OTf) ₃ | 20 | No conversion |
| 9 | OAc | Yb(OTf) ₃ | 20 | No conversion |

^a Reactions were carried out on 0.10 mmol scale with 1.5 equiv. of 13–15 in CH₂Cl₂ (0.05 M). ^b Isolated yields. ^c Reaction was carried out on 0.20 mmol scale with 1.05 equiv. of 14 in CH₂Cl₂ (0.50 M). ^d Reaction was carried out on 2.00 mmol scale with 1.05 equiv. of 14 in CH₂Cl₂ (0.50 M). ^e 0.2 M in CH₂Cl₂. Phth = phthalimide, Tf = trifluoromethylsulfonyl, PMP = *para* methoxyphenyl.



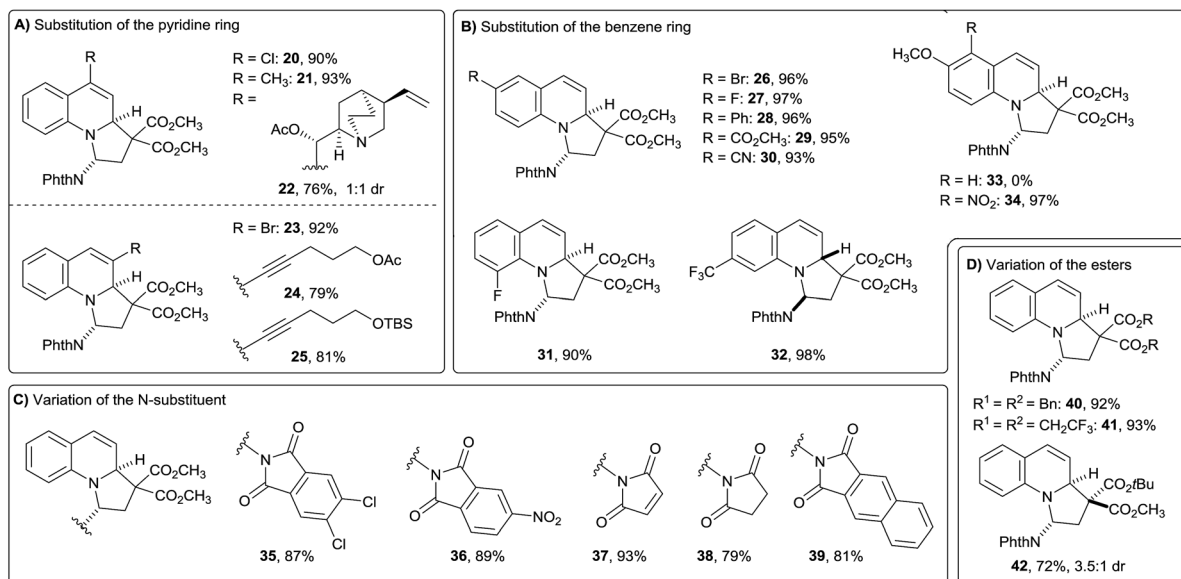


Fig. 2 Scope of the [3 + 2] annulation with quinolines. Reaction conditions: quinoline (0.20 mmol), DA-cyclopropane (0.21 mmol), Yb(OTf)₃ (5 mol%), CH₂Cl₂ (0.5 M). Unless noted otherwise products obtained with dr > 20 : 1. Phth = phthalimide, TBS = *tert*-butyldimethylsilyl.

reported for addition to pyridinium salts.^{4h} Ethyl nicotinate derivative **53** could not be obtained, but 3,4- and 3,5-diester substituted pyridines gave the desired products **54** and **55** in good yields. Alternatively, installation of a more electron-

withdrawing HFIP ester was also successful (product **56**). These active esters can be readily converted into different amides and esters.²¹ Other electron-withdrawing groups on the nicotinate also led to good yields (products **57** and **58**). Finally, nitro-substituted pyridines also furnished the desired products **59–61** in 74–80% yield.

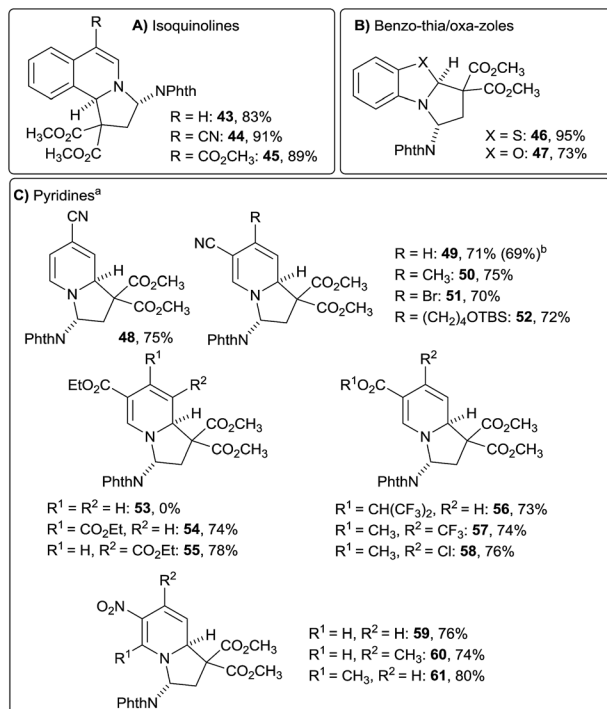
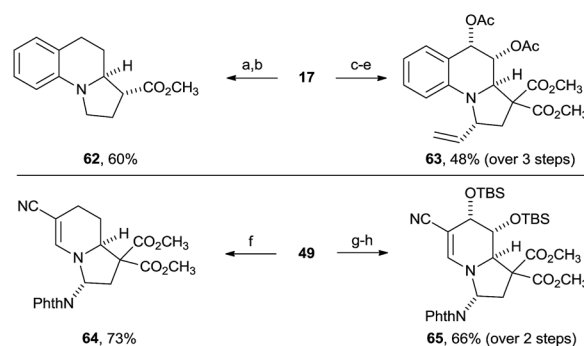


Fig. 3 Reaction conditions: N-heterocycle (0.20 mmol), **14** (0.21 mmol), Yb(OTf)₃ (5 mol%), CH₂Cl₂ (0.5 M). Unless noted otherwise products obtained with dr > 20 : 1. ^aChanges from normal reaction conditions: Yb(OTf)₃ (10 mol%), CH₂Cl₂ (1 M). ^b1 mmol scale. Phth = phthalimide, TBS = *tert*-butyldimethylsilyl.

2.3. Product functionalization

The obtained building blocks contain highly interesting functionalities for further modification, including in particular reactive alkenes and aminals. To further establish the synthetic



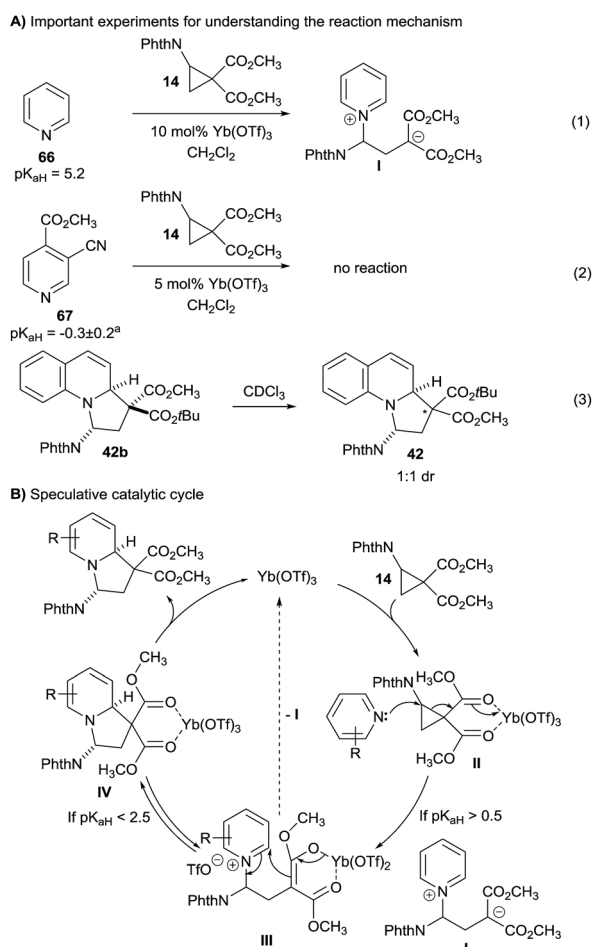
Scheme 4 Functionalization of products **17** and **49**. Reaction conditions: (a) H₂, Pd(OH)₂ (10% w/w), CH₃OH, 70%; (b) LiCl (5 equiv.), DMSO : H₂O 10 : 1, 140 °C, 85%; (c) OsO₄ (5 mol%), NMO·H₂O (1.2 equiv.), THF : acetone : H₂O (2 : 2 : 1); (d) Ac₂O (3 equiv.), DMAP (10 mol%), NEt₃ (4 equiv.), CH₂Cl₂, 71% dr > 20 : 1 (over 2 steps); (e) vinylMgBr (4 equiv.), ZnCl₂ (10 equiv.), THF, 50 °C, 68%, dr > 20 : 1; (f) H₂, Pd(OH)₂ (10% w/w), CH₃OH, 73%; (g) OsO₄ (5 mol%), NMO·H₂O (1.2 equiv.), acetone : H₂O (20 : 1), 0 °C; (h) TBSOTf, pyridine, CH₂Cl₂, 66%, dr > 20 : 1 (over 2 steps). Phth = phthalimide, TBS = *tert*-butyldimethylsilyl, NMO = *N*-methylmorpholine-*N*-oxide, THF = tetrahydrofuran, DMAP = *N,N*-dimethylpyridin-4-amine.



potential of the method, a few transformations of the dearomatization products were therefore examined (Scheme 4). Hydrogenation of the benzylic olefin and amination of tetrahydrobenzoindolizine **17** and removal of one methyl ester group was achieved using Pearlman's catalyst, followed by Krapcho decarboxylation to give amine **62** in 60% overall yield. The phthalimido and the diester groups can therefore be considered as traceless activating and directing groups for the annulation reaction.

Selective dihydroxylation of the benzylic olefin from the convex side of the molecule was possible (*dr* > 20 : 1). After acetylation of the alcohols, the amination was converted with high diastereoselectivity (*dr* > 20 : 1) into tertiary amine **63** through alkylation of the intermediary iminium with a vinyl zinc reagent, resulting in the stereoselective installation of four stereocenters around the tricyclic system.

Selective reduction of the more electron rich olefin of tetrahydroindolizine **49** furnished compound **64** in 73% yield. Moreover, selective dihydroxylation *via* osmium(viii) catalysis and subsequent silylation of the diol gave compound **65** in high yield and high diastereoselectivity (*dr* > 20 : 1). Our methodology is therefore highly suited for accessing polysubstituted indolizidine rings frequently encountered in natural products (Scheme 1).



Scheme 5 Key experiments and speculative mechanism. ^aPredicted with ACD Labs.

2.4. Speculative reaction mechanism

Three experiments gave first insights into the reaction mechanism (Scheme 5A):

(1) When pyridine (**66**) was reacted with cyclopropane **14** using ytterbium triflate as catalyst, the desired product was not obtained. Full conversion of cyclopropane **14** was observed, but no pure product could be isolated from the reaction mixture. Nevertheless, a molecular ion corresponding to zwitterion **I** could be detected by mass spectroscopy.

(2) When highly electron-poor pyridine **67** was used, no reaction was observed (eqn (2)).

(3) Quinolizine **42** could be isolated with 3.5 : 1 *dr* at the diester center. However, after separation the minor isomer **42a** equilibrated to a 1 : 1 mixture just upon standing in deuterated chloroform (eqn (3)).

Based on these experiments and the well-established activation of DA diester cyclopropanes with Lewis acids,^{11a} a first speculative mechanism can be proposed (Scheme 5B). Coordination of cyclopropane **14** by the Lewis acid led to activated intermediate **II**. Only sufficiently electron-rich pyridine ($pK_{aH} > 0.5$) are nucleophilic enough to react with this intermediate and give pyridinium **III**. At this point, reversible ring closure can occur to give coordinated product **IV**. The equilibrium lays on the product side for quinolines. For pyridines, this is the case only if the heterocycle is sufficiently electron poor ($pK_{aH} < 2.5$). If this is not the case, decoordination of the Lewis acid would free zwitterion **I**,²⁰ which could be detected by mass spectroscopy. The high diastereoselectivity observed in the reaction is probably due to the higher stability of the products having the phthalimido group in the convex face of the polycyclic systems (thermodynamic control). From **IV**, the catalytic cycle is then closed by a simple ligand exchange on ytterbium.

3. Conclusion

In summary, a highly efficient method for the preparation of tetrahydroindolizine derivatives by dearomative [3 + 2] annulation reactions of pyridines, isoquinolines or quinolines and 2-aminocyclopropanes was developed. The fine modulation of the reactivity by the phthalimido group was essential for the success of this process. Excellent yields, high diastereoselectivities and a very broad substrate scope was achieved by employing ytterbium(III) triflate as catalyst. The reaction proved to be scalable and further functionalization of the obtained products was easily possible, setting the base for the synthesis of more complex bioactive compounds.

Conflicts of interest

There are no conflicts to declare.

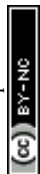
Acknowledgements

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Notes and references

- 1 J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139.
- 2 (a) F. Wong-Staal, G. Liu and M. Jeffrey, in *Antiviral Drugs: From Basic Discovery through Clinical Trials*, ed. W. M. Kazmierski, John Wiley & Sons, Inc., Hoboken, NJ, 2011, pp. 329–337; (b) S. J. F. Kaptein and J. Neyts, *Curr. Opin. Pharmacol.*, 2016, **30**, 1.
- 3 (a) R. M. Kariba, P. J. Houghton and A. Yenesew, *J. Nat. Prod.*, 2002, **65**, 566; (b) V. U. Ahmad, A.-u. Rahman, T. Rasheed and H.-u. Rehman, *Heterocycles*, 1987, **26**, 1251; (c) V. U. Ahmad and S. Iqbal, *Nat. Prod. Lett.*, 1993, **2**, 105.
- 4 Reviews: (a) S. P. Roche and J. A. Porco, *Angew. Chem., Int. Ed.*, 2011, **50**, 4068; (b) C.-X. Zhuo, W. Zhang and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 12662; (c) Q. Ding, X. Zhou and R. Fan, *Org. Biomol. Chem.*, 2014, **12**, 4807; selected examples: (d) K. Frisch, A. Landa, S. Saaby and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2005, **44**, 6058; (e) M. S. Taylor, N. Tokunaga and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2005, **44**, 6700; (f) Z. Sun, S. Yu, Z. Ding and D. Ma, *J. Am. Chem. Soc.*, 2007, **129**, 9300; (g) M. A. Fernandez-Ibanez, B. Macia, M. G. Pizzuti, A. J. Minnaard and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2009, **48**, 9339; (h) N. Christian, S. Aly and K. Belyk, *J. Am. Chem. Soc.*, 2011, **133**, 2878; (i) O. García Mancheño, S. Asmus, M. Zurro and T. Fischer, *Angew. Chem., Int. Ed.*, 2015, **54**, 8823; (j) G. Bertuzzi, A. Sinisi, L. Caruana, A. Mazzanti, M. Fochi and L. Bernardi, *ACS Catal.*, 2016, **6**, 6473; (k) K. Kubota, Y. Watanabe, K. Hayama and H. Ito, *J. Am. Chem. Soc.*, 2016, **138**, 4338; for intramolecular approaches, see: (l) Z.-P. Yang, Q.-F. Wu and S.-L. You, *Angew. Chem., Int. Ed.*, 2014, **53**, 6986; (m) Z.-P. Yang, Q.-F. Wu, W. Shao and S.-L. You, *J. Am. Chem. Soc.*, 2015, **137**, 15899.
- 5 For selected rare examples of other type of annulation processes, see: (a) R. Huisgen, M. Morikawa, K. Herbig and E. Brunn, *Chem. Ber.*, 1967, **100**, 1094; (b) O. Tsuge, S. Kanemasa and S. Takenaka, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 3320; (c) V. Nair, A. R. Sreekanth, N. Abhilash, M. M. Bhadbhade and R. C. Gonnade, *Org. Lett.*, 2002, **4**, 3575; (d) V. Nair, S. Devipriya and E. Suresh, *Tetrahedron*, 2008, **64**, 3567; (e) V. Nair, S. Devipriya and E. Suresh, *Synthesis*, 2008, **2008**, 1065; (f) A. Shaabani, A. H. Rezayan, A. Sarvary and H. R. Khavasi, *Tetrahedron Lett.*, 2008, **49**, 1469; (g) D. B. Huple, S. Ghorpade and R.-S. Liu, *Chem.–Eur. J.*, 2013, **19**, 12965; (h) T. Onnagawa, Y. Shima, T. Yoshimura and J.-i. Matsuo, *Tetrahedron Lett.*, 2016, **57**, 3050.
- 6 Selected reviews: (a) H.-U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151; (b) F. De Simone and J. Waser, *Synthesis*, 2009, 3353; (c) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504; (d) M. A. Cavitt, L. H. Phun and S. France, *Chem. Soc. Rev.*, 2014, **43**, 804; (e) H. K. Grover, M. R. Emmett and M. A. Kerr, *Org. Biomol. Chem.*, 2015, **13**, 655.
- 7 Selected examples: (a) J.-P. Qu, C. Deng, J. Zhou, X.-L. Sun and Y. Tang, *J. Org. Chem.*, 2009, **74**, 7684; (b) J.-P. Qu, Y. Liang, H. Xu, X.-L. Sun, Z.-X. Yu and Y. Tang, *Chem.–Eur. J.*, 2012, **18**, 2196; (c) F. de Nanteuil and J. Waser, *Angew. Chem., Int. Ed.*, 2011, **50**, 12075; (d) S. Racine, F. de Nanteuil, E. Serrano and J. Waser, *Angew. Chem., Int. Ed.*, 2014, **53**, 8484.
- 8 S. Chakrabarty, I. Chatterjee, B. Wibbeling, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2014, **53**, 5964.
- 9 Selected examples: (a) C. A. Carson and M. A. Kerr, *J. Org. Chem.*, 2005, **70**, 8242; (b) V. S. Korotkov, O. V. Larionov, A. Hofmeister, J. Magull and A. de Meijere, *J. Org. Chem.*, 2007, **72**, 7504; (c) R. Tombe, T. Kurahashi and S. Matsubara, *Org. Lett.*, 2013, **15**, 1791.
- 10 Selected examples: (a) X. Qi and J. M. Ready, *Angew. Chem., Int. Ed.*, 2008, **47**, 7068; (b) W. D. Mackay, M. Fistikci, R. M. Carris and J. S. Johnson, *Org. Lett.*, 2014, **16**, 1626; (c) F. G. Perrin, G. Kiefer, L. Jeanbourquin, S. Racine, D. Perrotta, J. Waser, R. Scopelliti and K. Severin, *Angew. Chem., Int. Ed.*, 2015, **54**, 13393; (d) S. Racine, B. Hegedüs, R. Scopelliti and J. Waser, *Chem.–Eur. J.*, 2016, **22**, 11997.
- 11 Selected examples: (a) P. D. Pohlhaus and J. S. Johnson, *J. Am. Chem. Soc.*, 2005, **127**, 16014; (b) P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li and J. S. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 8642; (c) A. T. Parsons and J. S. Johnson, *J. Am. Chem. Soc.*, 2009, **131**, 3122; (d) S. Xing, W. Pan, C. Liu, J. Ren and Z. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 3215; (e) F. Benfatti, F. de Nanteuil and J. Waser, *Chem.–Eur. J.*, 2012, **18**, 4844; (f) F. Benfatti, F. de Nanteuil and J. Waser, *Org. Lett.*, 2012, **14**, 386; (g) Y. Miyake, S. Endo, T. Moriyama, K. Sakata and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2013, **52**, 1758; (h) F. de Nanteuil, E. Serrano, D. Perrotta and J. Waser, *J. Am. Chem. Soc.*, 2014, **136**, 6239; (i) S. Racine, J. Vuilleumier and J. Waser, *Isr. J. Chem.*, 2016, **56**, 566.
- 12 Selected examples: (a) I. S. Young and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2003, **42**, 3023; (b) I. S. Young and M. A. Kerr, *Org. Lett.*, 2004, **6**, 139; (c) I. S. Young, J. L. Williams and M. A. Kerr, *Org. Lett.*, 2005, **7**, 953; (d) C. A. Carson and M. A. Kerr, *Angew. Chem., Int. Ed.*, 2006, **45**, 6560; (e) K. Sapeta and M. A. Kerr, *J. Org. Chem.*, 2007, **72**, 8597; (f) M. P. Sibi, Z. H. Ma and C. P. Jasperse, *J. Am. Chem. Soc.*, 2005, **127**, 5764; (g) Y. B. Kang, X. L. Sun and Y. Tang, *Angew. Chem., Int. Ed.*, 2007, **46**, 3918.
- 13 Selected examples: (a) M. A. Kerr and R. G. Keddy, *Tetrahedron Lett.*, 1999, **40**, 5671; (b) D. B. England, T. D. O. Kuss, R. G. Keddy and M. A. Kerr, *J. Org. Chem.*, 2001, **66**, 4704; (c) C. Venkatesh, P. P. Singh, H. Ila and H. Junjappa, *Eur. J. Org. Chem.*, 2006, **2006**, 5378; (d) B. Bajtos, M. Yu, H. Zhao and B. L. Pagenkopf, *J. Am. Chem. Soc.*, 2007, **129**, 9631; (e) M. M. A. R. Moustafa and B. L. Pagenkopf, *Org. Lett.*, 2010, **12**, 3168; (f) S. M. Wales, M. M. Walker and J. S. Johnson, *Org. Lett.*, 2013, **15**, 2558; (g) H. Xiong, H. Xu, S. Liao, Z. Xie and Y. Tang, *J. Am. Chem. Soc.*, 2013, **135**, 7851; (h) C. C. Dulin, K. L. Murphy and K. A. Nolin, *Tetrahedron Lett.*, 2014, **55**, 5280.



- 14 D.-C. Wang, M.-S. Xie, H.-M. Guo, G.-R. Qu, M.-C. Zhang and S.-L. You, *Angew. Chem., Int. Ed.*, 2016, **55**, 14111.
- 15 C. W. Bird, *Tetrahedron*, 1996, **52**, 9945.
- 16 (a) N. A. Morra, C. L. Morales, B. Bajtos, X. Wang, H. Jang, J. Wang, M. Yu and B. L. Pagenkopf, *Adv. Synth. Catal.*, 2006, **348**, 2385; (b) J. Liu, L. Zhou, W. Ye and C. Wang, *Chem. Commun.*, 2014, **50**, 9068.
- 17 F. González-Bobes, M. D. B. Fenster, S. Kiau, L. Kolla, S. Kolotuchin and M. Soumeillant, *Adv. Synth. Catal.*, 2008, **350**, 813.
- 18 X-ray data is available at the Cambridge Crystallographic Data Center (CCDC number: 1556244).† The relative configuration for other compounds was assumed to be the same on the basis of the similarity in their NMR-spectra.
- 19 Preliminary investigations showed that an enantioselective process should be possible, but highly challenging to develop, as so far no enantioselectivity higher than 18% was obtained. See Table S8 in the ESI.†
- 20 (a) S. Danishefsky and R. K. Singh, *J. Am. Chem. Soc.*, 1975, **97**, 3239; (b) E. M. Budynina, O. A. Ivanova, E. B. Averina, T. S. Kuznetsova and N. S. Zefirov, *Tetrahedron Lett.*, 2006, **47**, 647.
- 21 (a) J.-M. Vatele, *Synlett*, 2015, **26**, 2280; (b) Y. Wang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2017, **56**, 3191.

