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

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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 tetrahydroindolizine derivatives. The products were obtained with high diastereoselectivities (dr > 20 : 1) as *anti*-isomers. Additionally, the formed aminals 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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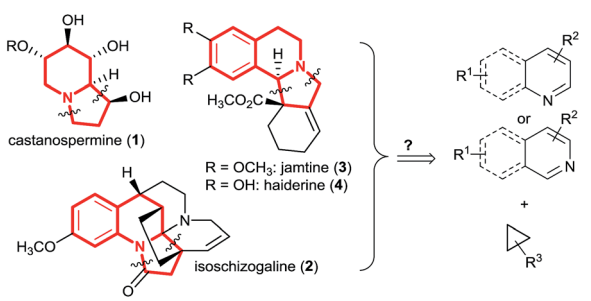
1. Introduction

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 jamtine (**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 compounds[11] and nitrones.[12] However, dearomative [3 + 2] annulation reactions were only intensively studied with indoles[13] 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.

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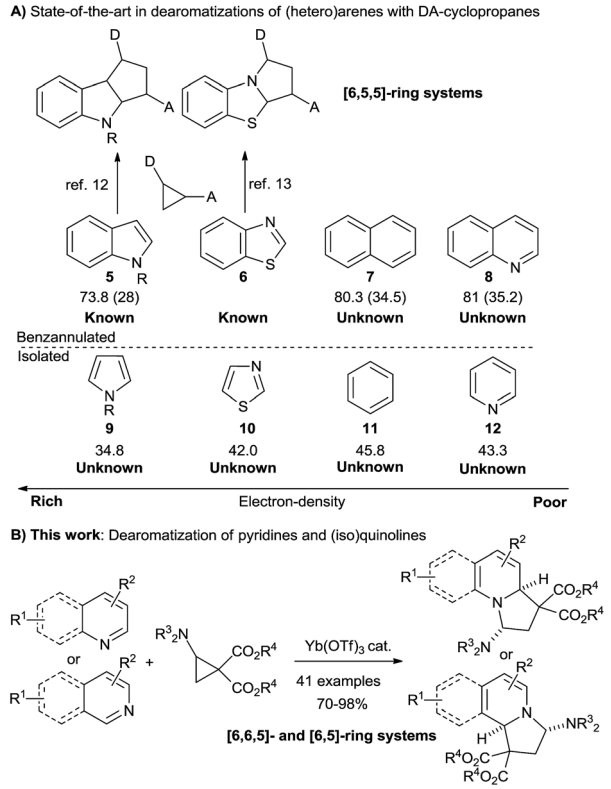
‡ Dr Chakrabarty has decided to stop his scientific career and cannot be contacted any more. He therefore did not see the final version of this manuscript. Based on his important contribution to the project, both J. P. and J. W. agree to include him as co-author and are convinced that he would agree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

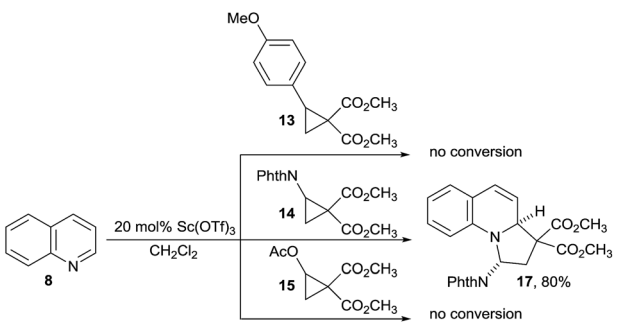
Herein we describe the dearomative [3 + 2] annulation of N-heterocycles with aminocyclopropanes to generate tetrahydroindolizines with high yield and stereoselectivity. Key for success were the exceptional properties of imido-substituted DA diester cyclopropanes, as other types of donor groups were not successful. A broad substrate scope including pyridines, quinolines, and isoquinolines is presented. The obtained aminals 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 diazomalonates 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**).

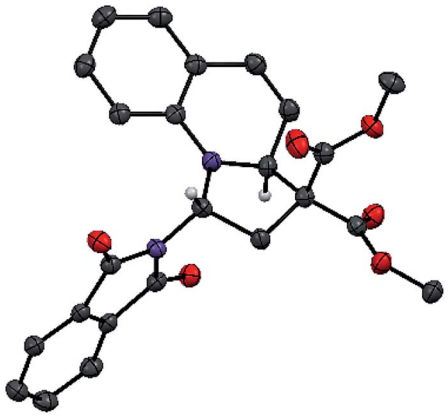


Fig. 1 Structure of compound **17** as determined by X-ray analysis. Some hydrogen atoms are omitted for clarity.

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**)

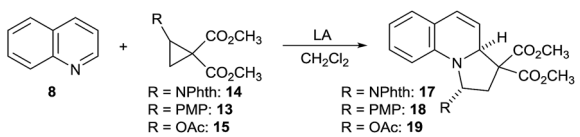
- Highly basic tertiary amines (product **22**).

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.[20] 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 CH_2Cl_2 (0.05 M). [b] Isolated yields. [c] Reaction was carried out on 0.20 mmol scale with 1.05 equiv. of **14** in CH_2Cl_2 (0.50 M). [d] Reaction was carried out on 2.00 mmol scale with 1.05 equiv. of **14** in CH_2Cl_2 (0.50 M). [e] 0.2 M in CH_2Cl_2. Phth = phthalimide, Tf = trifluoromethylsulfonyl, PMP = *para* methoxyphenyl.

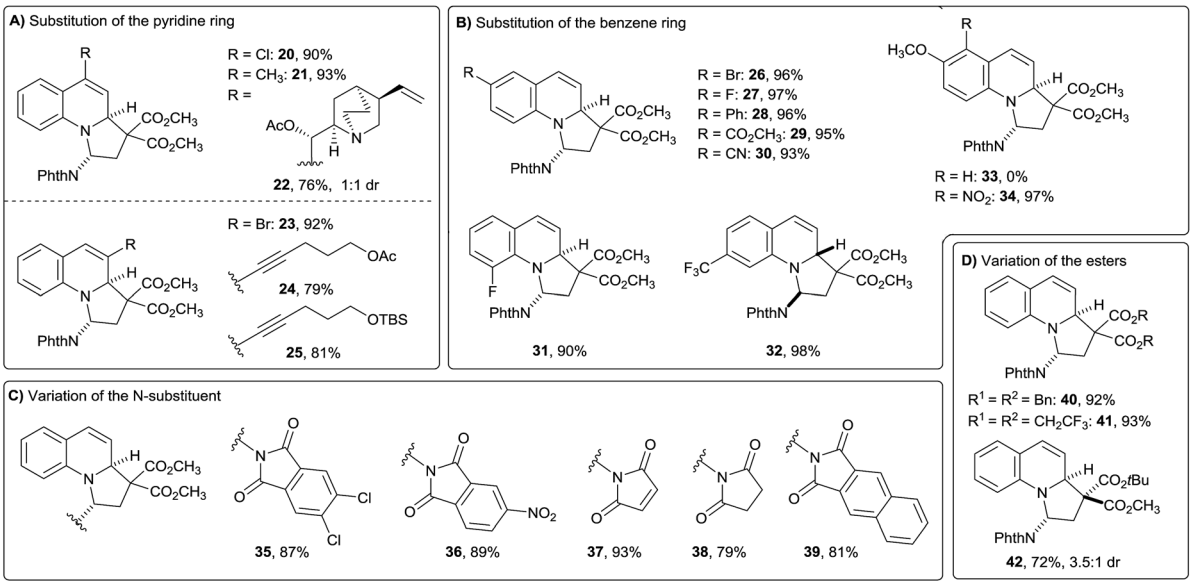


Fig. 2 Scope of the [3 + 2] annulation with quinolines. Reaction conditions: quinoline (0.20 mmol), DA-cyclopropane (0.21 mmol), $Yb(OTf)_3$ (5 mol%), CH_2Cl_2 (0.5 M). Unless noted otherwise products obtained with dr > 20 : 1. Phth = phthalimide, TBS = *tert*-butyldimethylsilyl.

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.

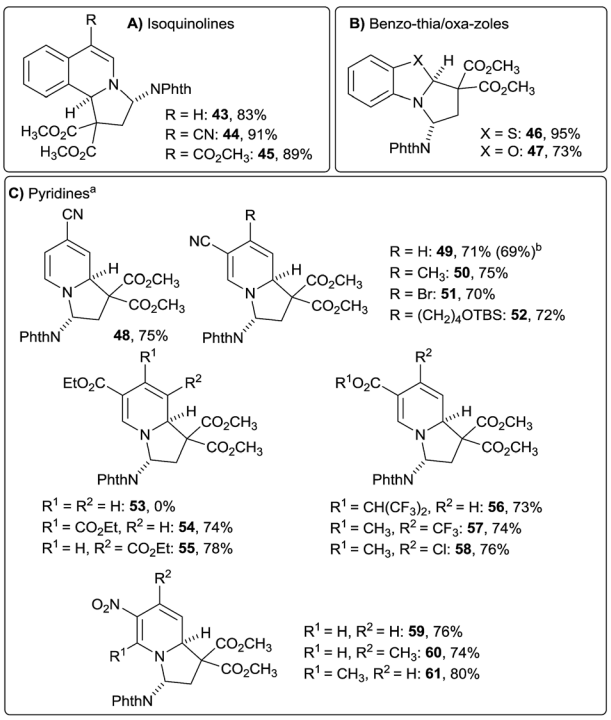
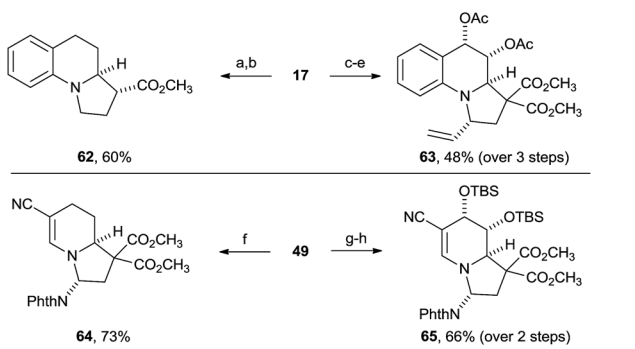


Fig. 3 Reaction conditions: N-heterocycle (0.20 mmol), **14** (0.21 mmol), $Yb(OTf)_3$ (5 mol%), CH_2Cl_2 (0.5 M). Unless noted otherwise products obtained with dr > 20 : 1. [a]Changes from normal reaction conditions: $Yb(OTf)_3$ (10 mol%), CH_2Cl_2 (1 M). [b]1 mmol scale. Phth = phthalimide, TBS = *tert*-butyldimethylsilyl.

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

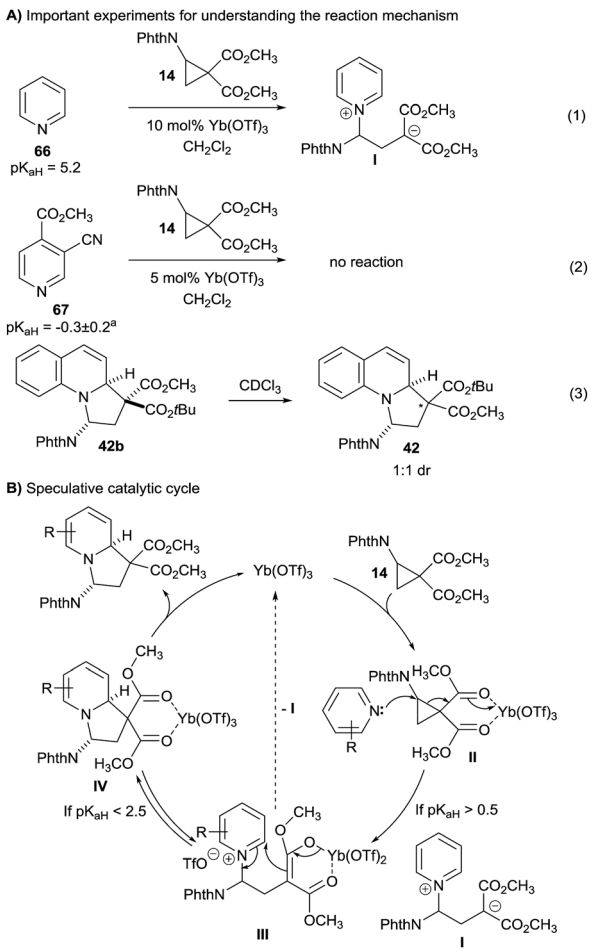


Scheme 4 Functionalization of products **17** and **49**. Reaction conditions: (a) H_2, $Pd(OH)_2$ (10% w/w), CH_3OH, 70%; (b) LiCl (5 equiv.), DMSO : H_2O 10 : 1, 140 °C, 85%; (c) OsO_4 (5 mol%), NMO·H_2O (1.2 equiv.), THF : acetone : H_2O (2 : 2 : 1); (d) Ac_2O (3 equiv.), DMAP (10 mol%), NEt_3 (4 equiv.), CH_2Cl_2, 71% dr > 20 : 1 (over 2 steps); (e) vinylMgBr (4 equiv.), $ZnCl_2$ (10 equiv.), THF, 50 °C, 68%, dr > 20 : 1; (f) H_2, $Pd(OH)_2$ (10% w/w), CH_3OH, 73%; (g) OsO_4 (5 mol%), NMO·H_2O (1.2 equiv.), acetone : H_2O (20 : 1), 0 °C; (h) TBSOTf, pyridine, CH_2Cl_2, 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 aminal 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 aminal 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. [a]Predicted 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 the detected by mass spectroscopy. The high diastereoselectivity observed in the reaction is probably due to the higher stability of the products having the phthalimide 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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