Current Literature Seminar

Feb. 16, 08

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Concise Enantioselective Total Syntheses of (+)-Homochelidonine, (+)-Chelamidine, (+)-Chelidonine, (+)-Chelamine and (+)-Norchelidonine via a Pd (II)-catalyzed Ring-Opening Strategy

Mark Lautens *et. al.*, *Chemistry- A European Journal*, **2008**, *Early View*

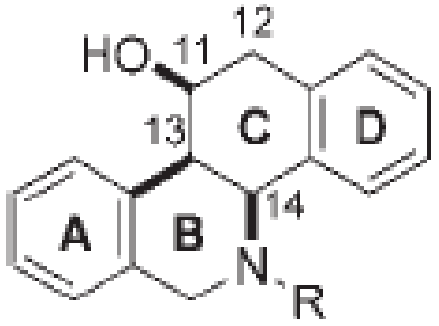
Abstract:

Five for the price of one: five natural products with one ring-opening reaction.

- New enantioselective syntheses of the B/C hexahydrobenzo[c]phenanthridine alkaloids (+)-homochelidonine, (+)-chelamidine, (+)-chelidonine, (+)-chelamine, and (+)-norchelidonine are described.

✓Our rapid and convergent route to this class of natural products involved the development and application of a Pd (II)-catalyzed asymmetric ring-opening reaction of a mesoazabicyclic alkene with an aryl boronic acid as the key step.

✓ By screening a variety of functionalized ortho-substituted aryl boronic acids, chiral ligands and reaction conditions we were able to prepare the requisite cis-1-amino-2-aryldihydronaphthalenes in high yield and in up to 90% ee.



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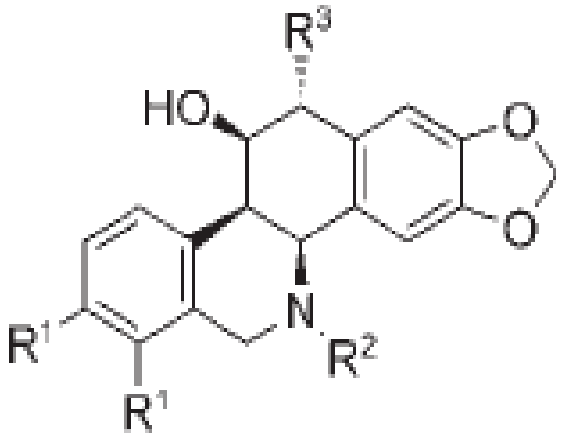


(+)-homochelidonine (**2**): R^1 = OMe, R^2 = Me, R^3 = H

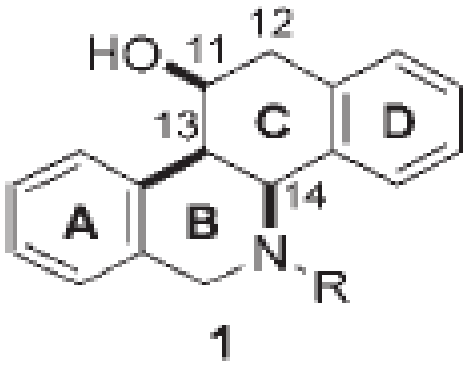
(+)-chelamidine (**3**): R^1 = OMe, R^2 = Me, R^3 = OH

(+)-chelidonine (**4**): R^1 = OCH_2O, R^2 = Me, R^3 = H

(+)-chelamine (**5**): R^1 = OCH_2O, R^2 = Me, R^3 = OH

(+)-norchelidonine (**6**): R^1 = OCH_2O, R^2 = H, R^3 = H

Figure 1. Structures of some B/C hexahydrobenzo[*c*]phenanthridine alkaloids.



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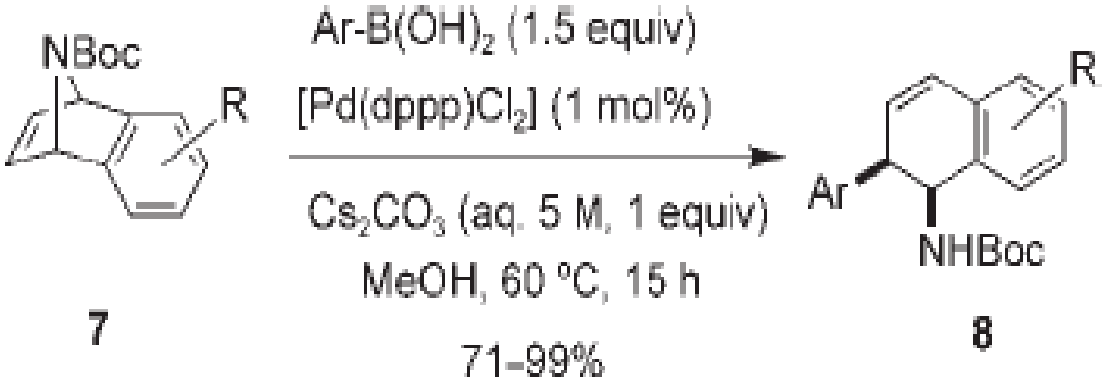
- Isoquinoline alkaloids, occur naturally in papaveraceous plants.
- chelidonine has received the most attention. Isolated from *Chelidonium majus L*. as early as 1839.
- Chelidonine has a range of proposed pharmacological activities including tubulin interaction within target cells causing mitotic arrest.
- Chelidonine is also a major component of the drug Ukrain, a semisynthetic •antitumor preparation derived from *C. majus* alkaloids.
- O-Acyl and O-alkyl derivatives of chelidonine have also shown antinociceptive and antiserotoninergic effects, not reported for the parent alkaloid.

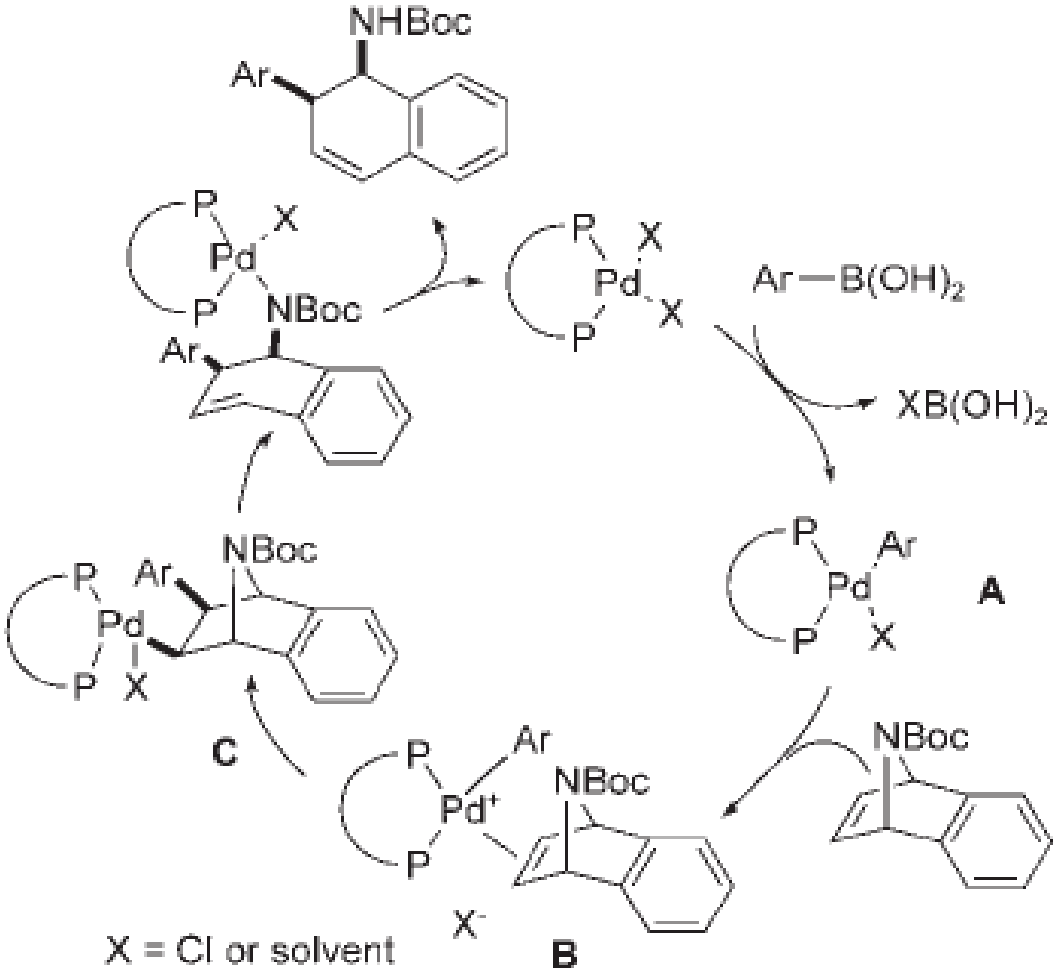
Previous reports:

1. a) I. Ninomiya, *et. al* , *Heterocycles* **1977**, *7*, 137; *J. Chem. Soc. Perkin Trans. 1*, **1983**, 2171; b) M.Hanaoka, *et. al*. *Tetrahedron Lett.* **1985**, *26*, 5163; c) M. Yoshida *et. al*. *Tetrahedron Lett.* **2002**, *43*, 6751.
2. a) K.Keller, *J. Am. Chem. Soc.* **1971**, *93*, 3836; b) M. Cushman, *et. al*. *Tetrahedron Lett.* **1980**, *21*, 3845; *J. Org. Chem.* **1980**, *45*, 5067; c) C. Robbiani, *Helv. Chim. Acta* **1983**, *66*, 1119; d) M.Hanaoka, et. al *Chem. Lett.* **1986**, 739.

Synthesis of cis-1-amino-2-aryldihydronaphthalenes:

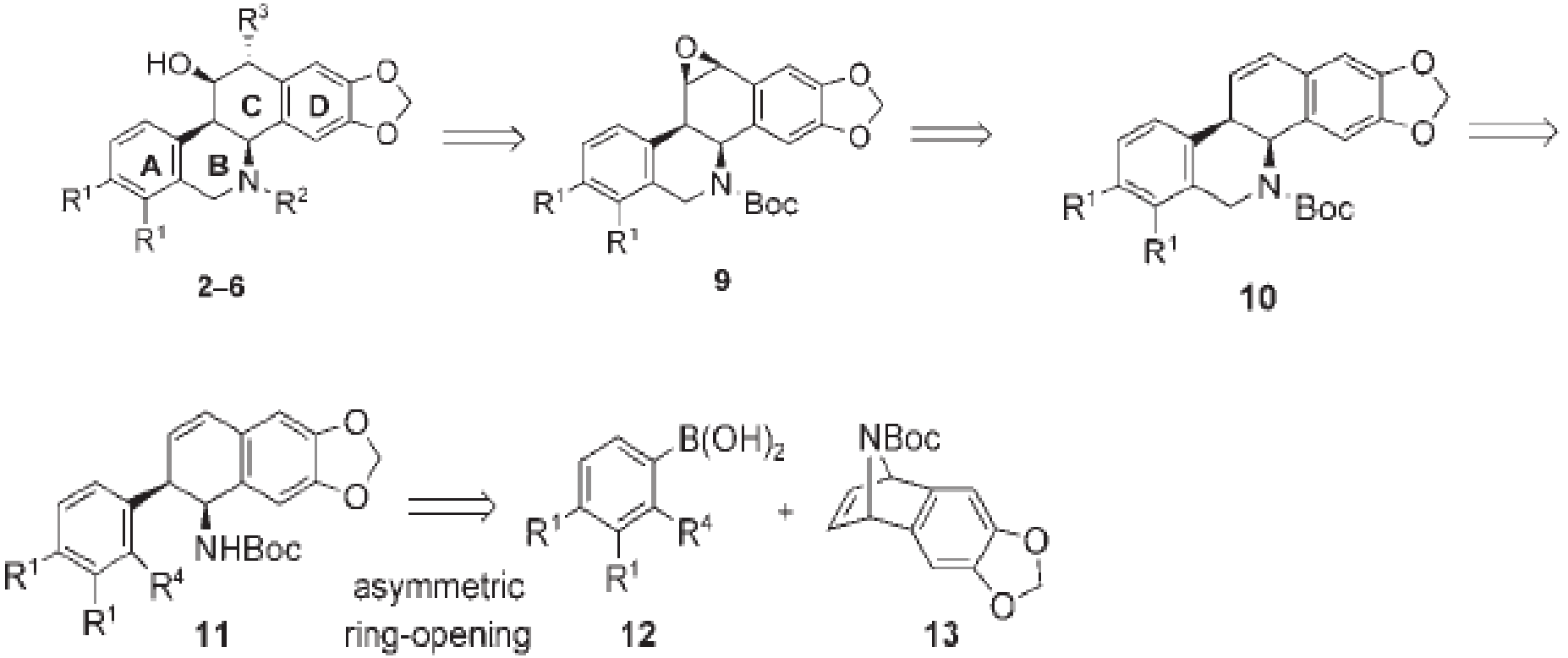


Scheme 1. Pd^{II}-catalyzed ring-opening of azabicyclic alkenes with boronic acids. Boc = *tert*-butyl carbamate. dppp = propane-1,3-diylbis(diphenylphosphane).

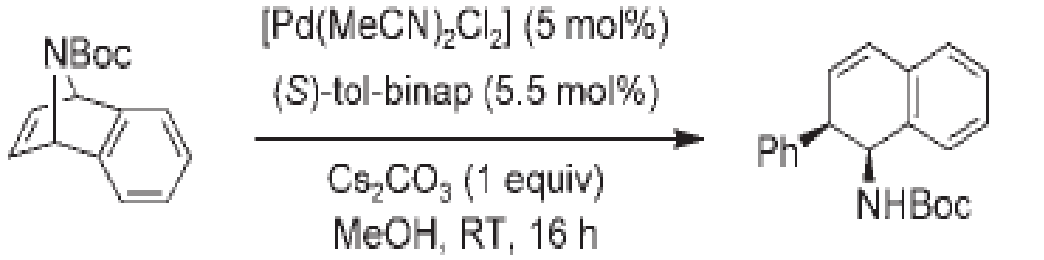


Scheme 2. Proposed catalytic cycle for Pd^{II}-catalyzed ring-opening of aza-bicyclic alkenes with aryl boronic acids.

Retrosynthetic analysis:



Assessing the feasibility of an enantioselective ring-opening reaction: Synthesis of key intermediates



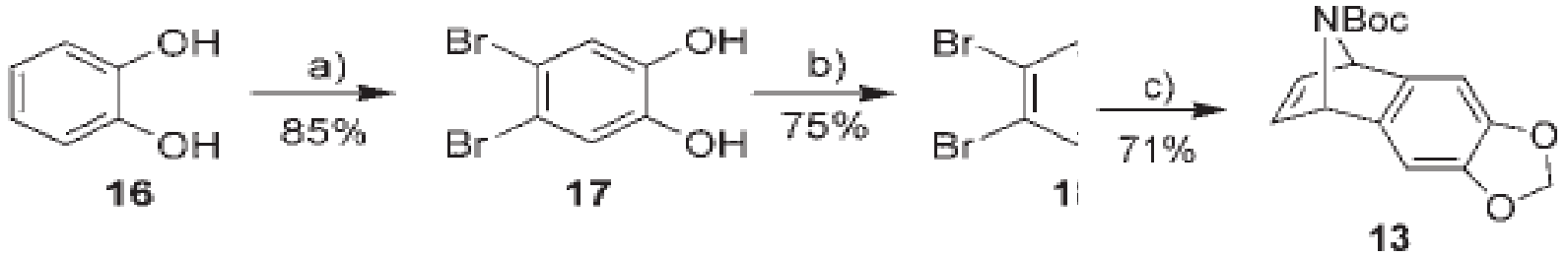
14 15

100% conversion

60% *ee*

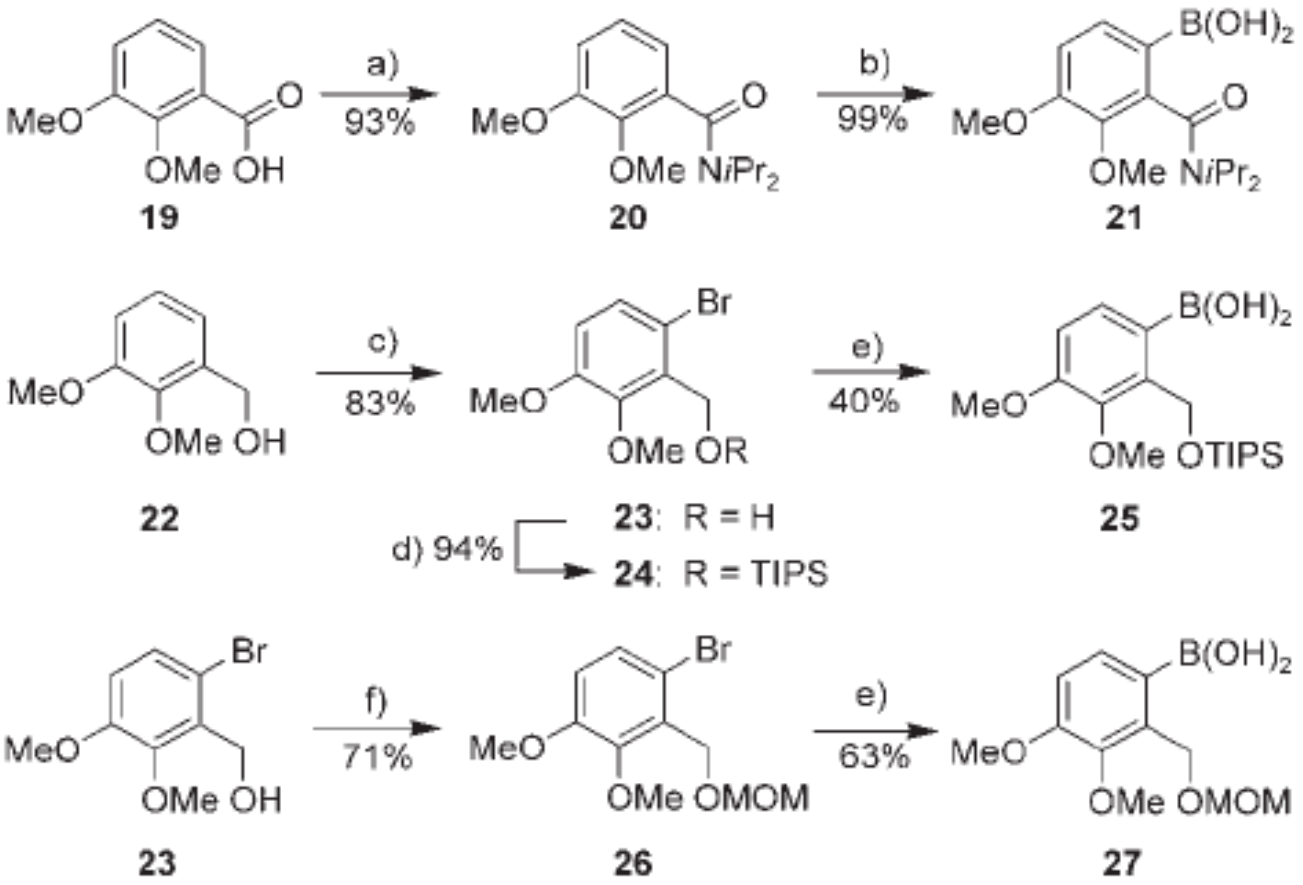
Scheme 4. Asymmetric ring-opening of azabicyclic alkene **14** with $PhB(OH)_2$. binap = 2,2′bis(diphenylphosphanyl)-1,1′-binaphthyl.

Synthesis of azabicyclic alkenes:



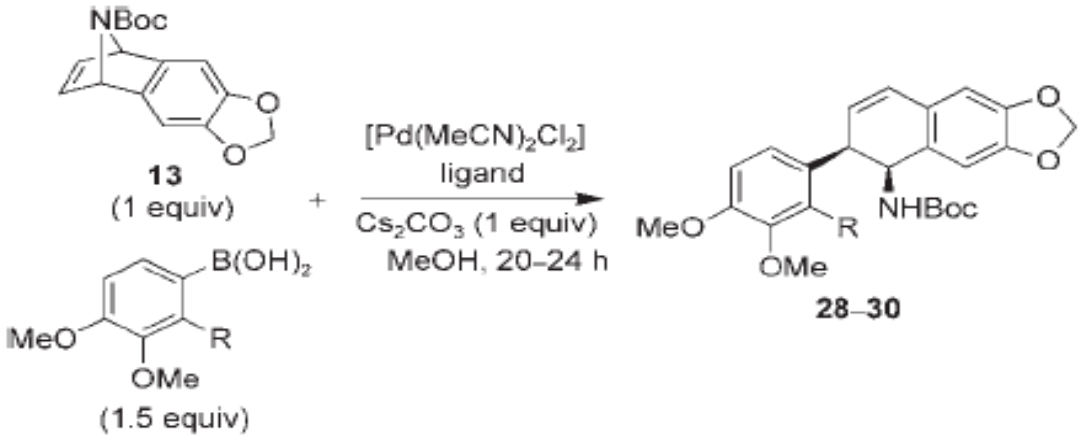
16 17 1 13

Scheme 5. Synthesis of *N*-Boc azabicycle **13** a) Br_2, $CHCl_3$, RT, 20 h; b) $ClCH_2Br$, Cs_2CO_3, DMF, 110 °C, 3 h; c) *N*-Boc pyrrole, *n*BuLi, PhMe, −78 °C to RT, 20 h. DMF = *N*,*N*-dimethylformamide, RT = room temperature.



Scheme 6. Synthesis of boronic acids **21**, **25** and **27**: a) $(COCl)_2$, CH_2Cl_2, cat. DMF, RT, 2 h, then iPr_2NH, Et_3N, THF, 17 h; b) *s*BuLi, TMEDA, THF, −78°C, 1 h then $B(OMe)_3$, −78°C to RT, 18 h then NH_4Cl (aq); c) NBS, THF, RT, 30 min; d) TIPSCl, imidazole, DMF, RT, 17 h; e) *n*BuLi, THF, −78°C, 35 min, then $B(OiPr)_3$, −78°C to RT, 18 h, then NH_4Cl (aq); f) $CH_2(OMe)_2$, LiBr, *p*-TsOH, RT, 24 h. THF = tetrahydrofuran, TMEDA = tetramethylethylenediamine, NBS = *N*-bromosuccinimide, TIPS = triisopropylsilyl, Ts = toluenesulfonyl, MOM = methoxymethyl.

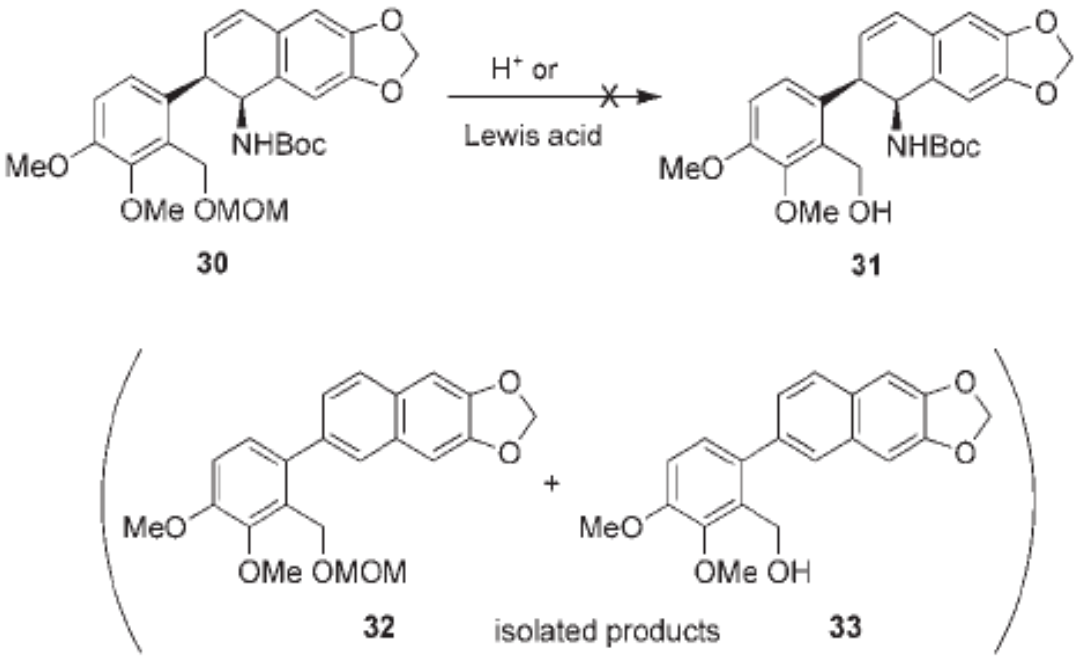
Table 1. Evaluating boronic acids in the enantioselective ring-opening reaction.



Entry	Boronic acid	R	Ligand	Product	Yield [%][c]	*ee* [%][d]
1[a]	**21**	C(O)N*i*Pr$_2$	dppp	**28**	81[e]	–
2[b]	**21**	C(O)N*i*Pr$_2$	(*S*)-tol-binap	**28**	43[e]	88
3[a]	**25**	CH$_2$OTIPS	dppp	**29**	55	–
4[b]	**25**	CH$_2$OTIPS	(*S*)-tol-binap	**29**	29	42
5[a]	**27**	CH$_2$OMOM	dppp	**30**	82	–
6[b]	**27**	CH$_2$OMOM	(*S*)-tol-binap	**30**	90	91

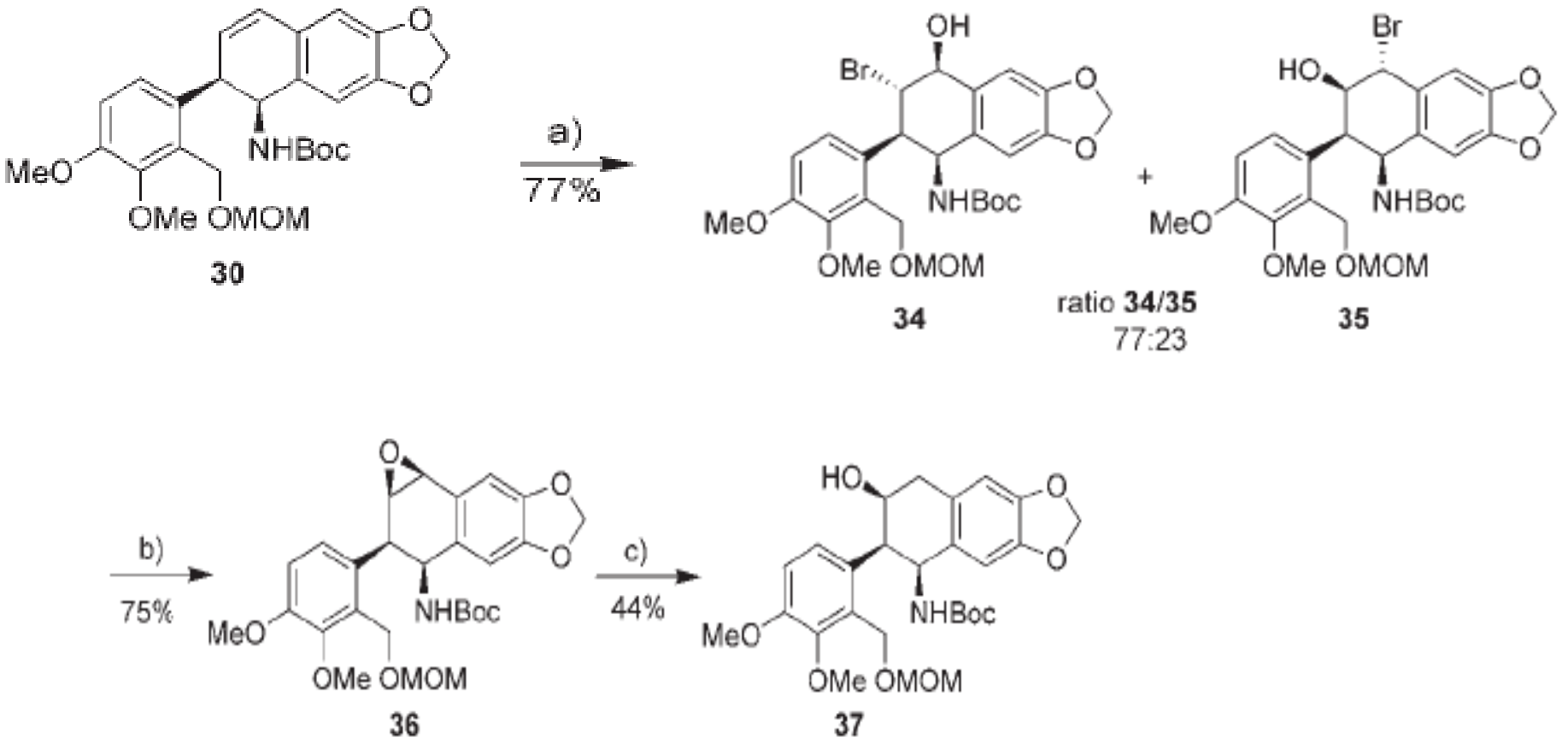
[a] 1 mol% $[Pd(MeCN)_2Cl_2]$, 1 mol% ligand, reaction carried out at 60°C. [b] 5 mol% $[Pd(MeCN)_2Cl_2]$, 5.5 mol% ligand, reaction carried out at RT. [c] Isolated yield unless otherwise stated. [d] Determined by chiral HPLC. [e] ^{1}H NMR yield using mesitylene as internal standard.

Attempted selective deprotection of the MOM group:



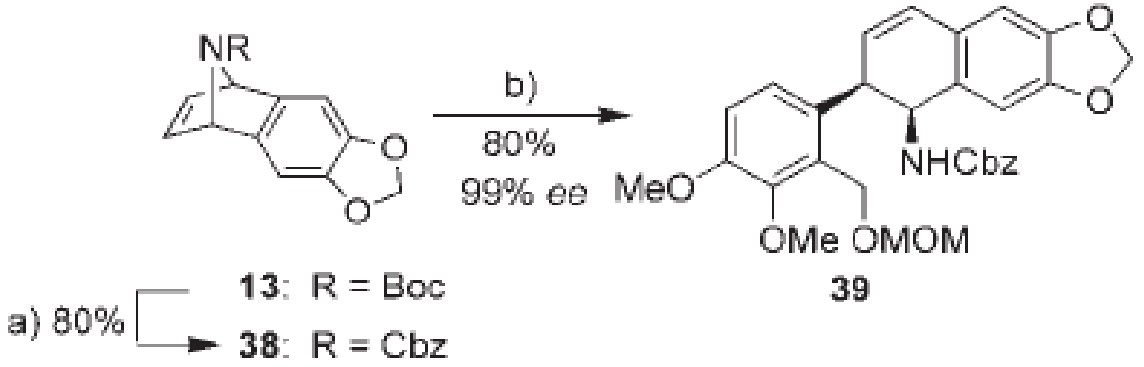
Scheme 7. Attempted selective removal of the MOM group.

Elaboration of the alkene:

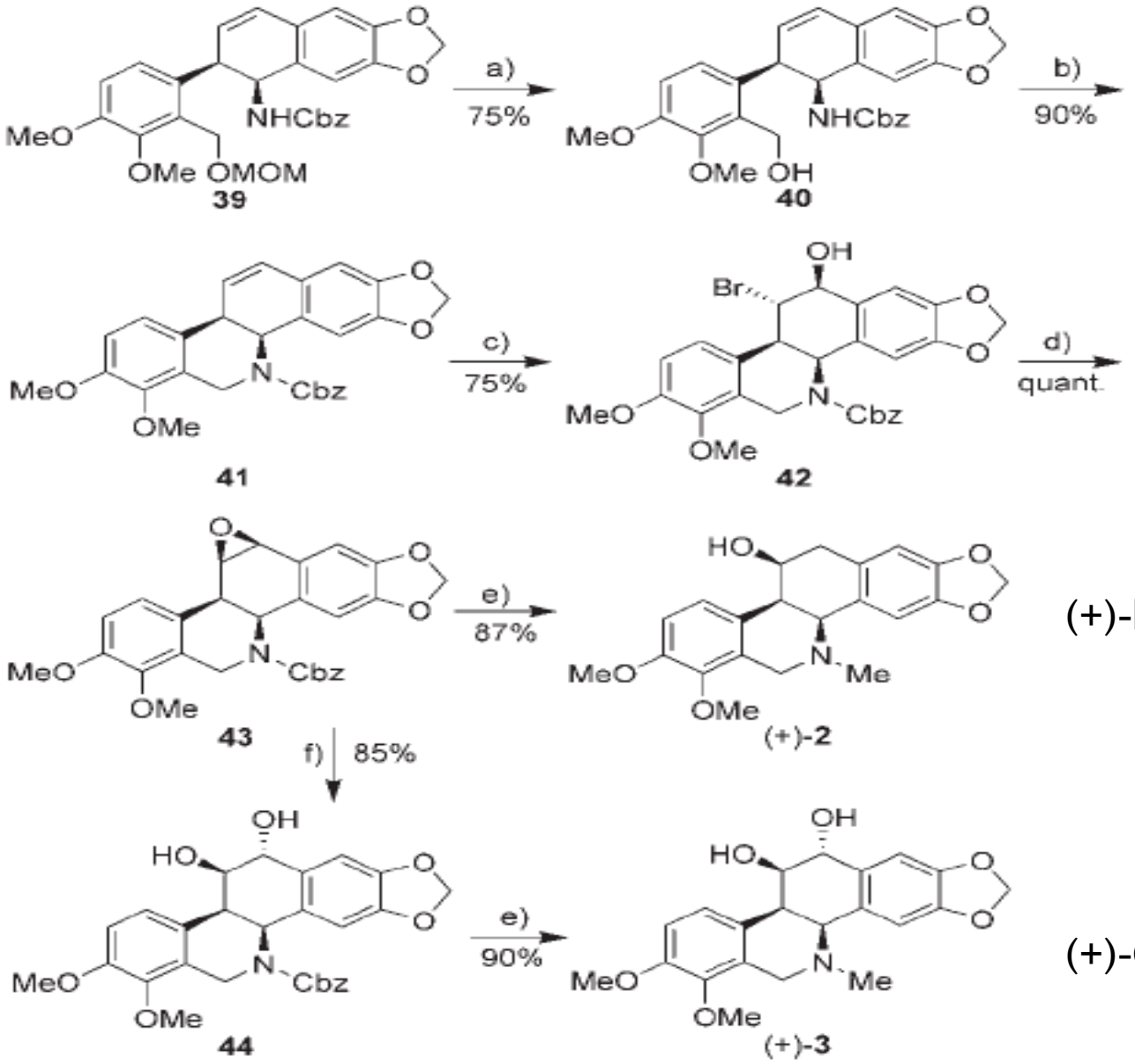


Scheme 8. Installation of the *syn*-hydroxy group: a) NBS, H_2O, THF, RT, 90 min; b) KO*t*Bu, THF, −78°C, 30 min; c) $LiAlH_4$, Et_2O, RT, 6 h.

Completion of the synthesis of (+)-homochelidonine and (+)-chelamidine:



Scheme 9. Synthesis of dihydronaphthalene **39**: a) TMSI, NEt_3, CH_2Cl_2, reflux, 15 min, then CbzCl, RT, 3 h; b) $[Pd(MeCN_2)Cl_2]$ (5 mol %), (*S*)-tol-binap (5.5 mol %), **27**, Cs_2CO_3, MeOH, RT, 6 h. TMS = trimethylsilyl, Cbz = benzyloxycarbonyl.

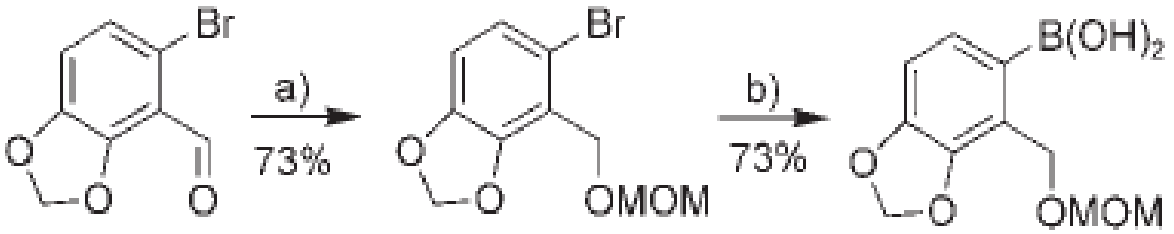


(+)-homochelidonine

(+)-Chelamidine

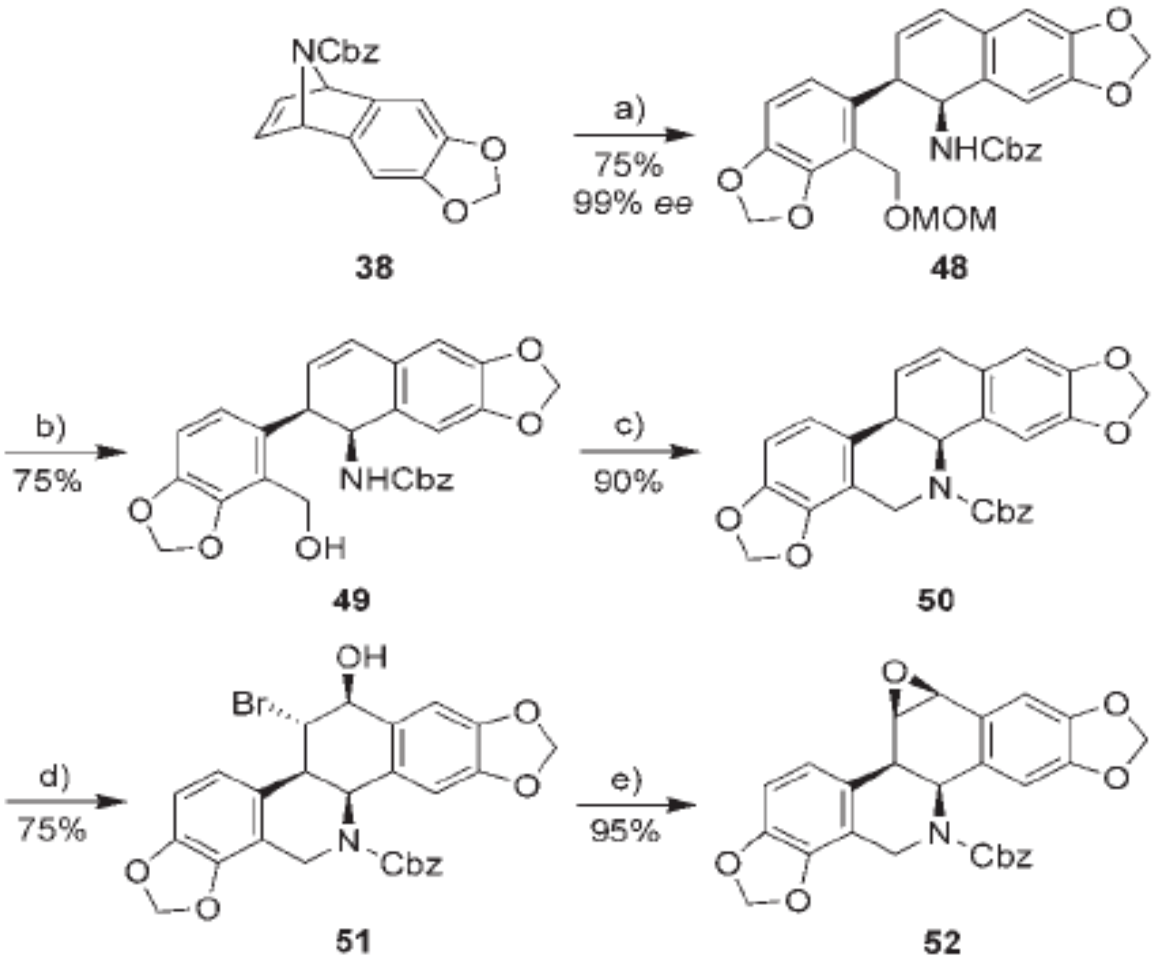
Scheme 10. Completion of the synthesis of (+)-homochelidonine (**2**) and (+)-chelamidine (**3**): a) HCl, *i*PrOH/THF, RT, 8 h; b) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 1 h, then NaH, DMF, 0 °C, 3 h; c) NBS, H_2O, THF, RT, 90 min; d) KO*t*Bu, THF, −78 °C, 30 min; e) $LiAlH_4$, 1,4-dioxane, reflux, 18 h; f) H_2O, cat. $BiCl_3$, MeCN, 0 °C, 30 min.

Syntheses of (+)-chelidonine, (+)-chelamine and (+)-norchelidonine:

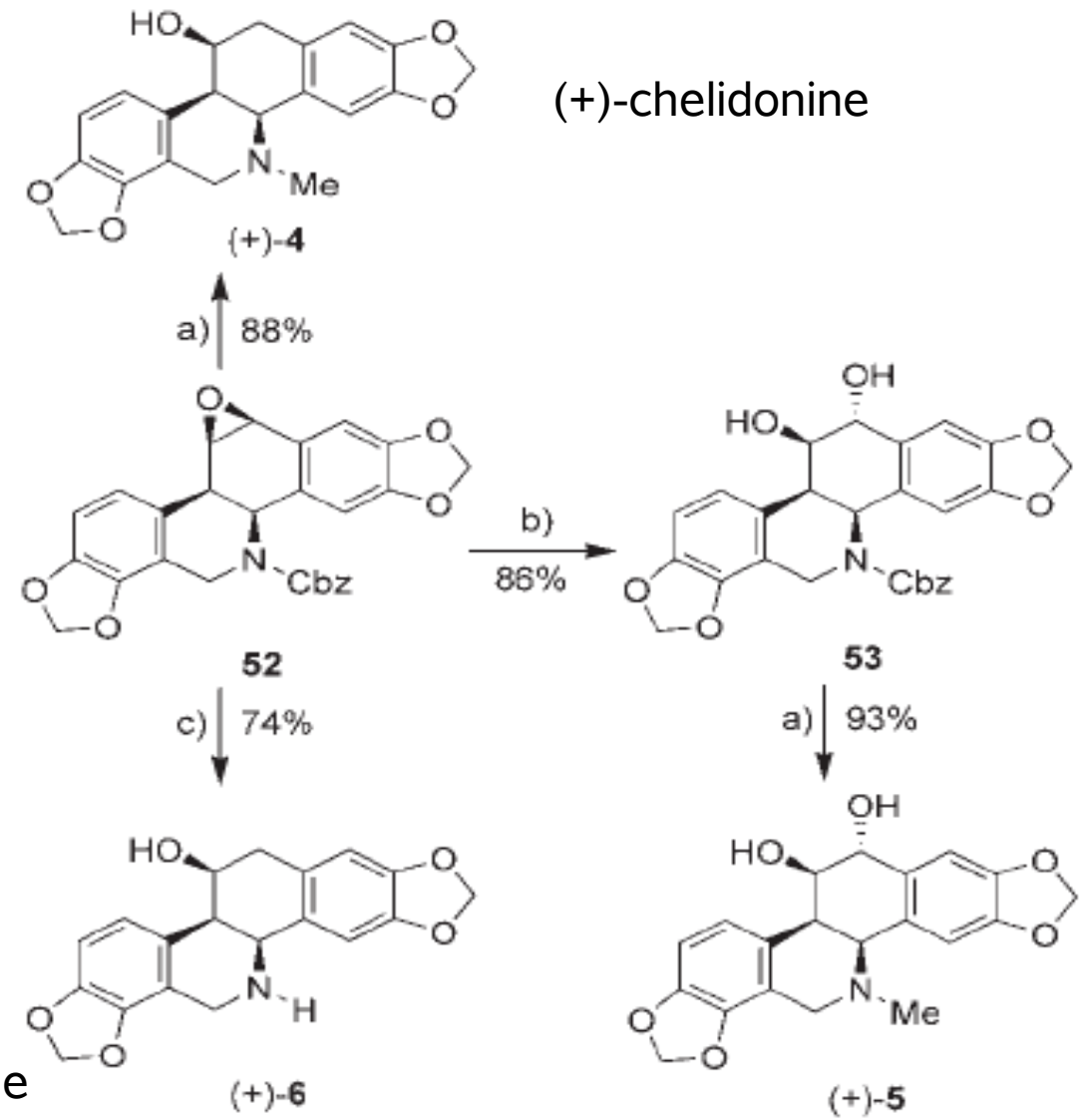


45 **46** **47**

Scheme 11. Synthesis of boronic acid **47**: a) $NaBH_4$, MeOH, RT, 1 h then $CH_2(OMe)_2$, LiBr, *p*-TsOH, RT, 15 h; b) *n*BuLi, THF, −78°C 45 min, then $B(OiPr)_3$, −78°C to RT, 18 h, then NH_4Cl (aq).



Scheme 12. Synthesis of key epoxide intermediate **52**: a) $Pd(MeCN_2)Cl_2$ (5 mol%), (*S*)-tol-BINAP (5.5 mol%), **47**, Cs_2CO_3, MeOH, RT, 6 h; b) HCl, *i*PrOH/THF, RT, 8 h; c) CBr_4, PPh_3, CH_2Cl_2, 0°C, 1 h, then NaH, DMF, 0°C, 3 h; d) NBS, THF/H_2O, RT, 90 min; e) KO*t*Bu, THF, –78°C, 30 min.



(+)-chelidonine

(+)-chelamine

(+)-norchelidonine

Scheme 13. Completion of the synthesis of (+)-chelidonine (**4**), (+)-chelamine (**5**) and (+)-norchelidonine (**6**): a) $LiAlH_4$, 1,4-dioxane, reflux 18 h; b) H_2O, cat. $BiCl_3$, MeCN, 0 °C, 30 min; c) 1 atm H_2, cat. Pd/C, EtOH, RT, 2 h.

Conclusion

In summary, we have developed a new and general strategy for the synthesis of the hexahydrobenzo[c]phenanthridine alkaloids with a novel and highly enantioselective PdII-catalyzed ring-opening reaction of a meso-azabicyclic alkene with an aryl boronic acid as the key step.In this way, we have demonstrated the power of this methodology for the first time in natural product synthesis and completed the first enantioselective total syntheses of (+)-homochelidonine, (+)-chelamidine, (+)-chelidonine, (+)-chelamine and (+)-norchelidonine.Due to the convergent nature of the synthesis it is now possible to prepare structural analogues of the hexahydrobenzo[c]phenanthridine alkaloids with potentially improved pharmacological properties.