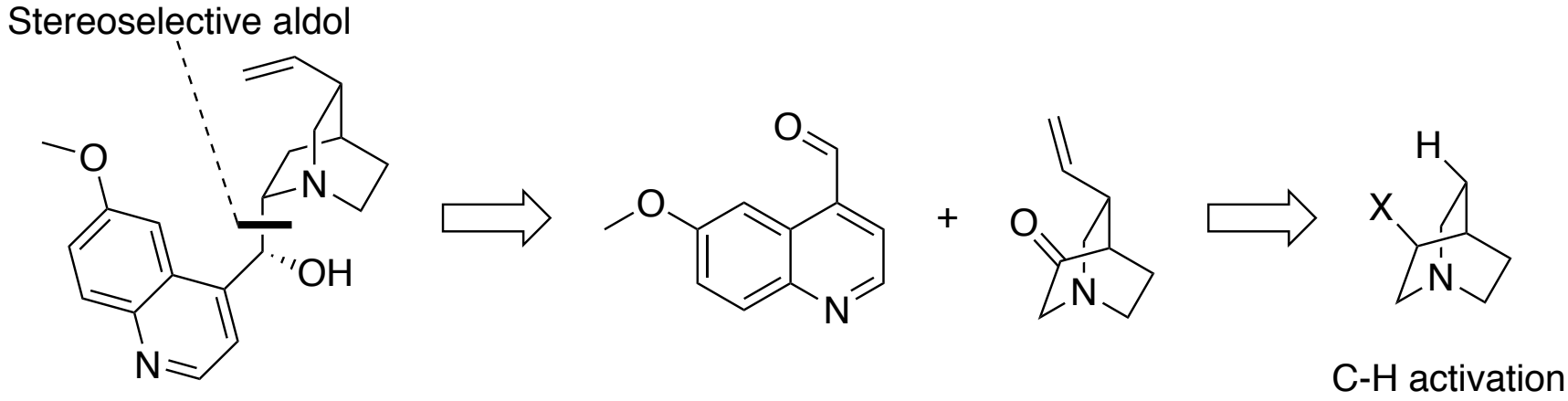
C-H Activation Enables a Concise Total Synthesis of Quinine and Analogues with Enhanced Antimalarial Activities



Nuno Maulide et. al., *Angew. Chem. Int. Ed*. 10.1002/anie.201804551

Quinine

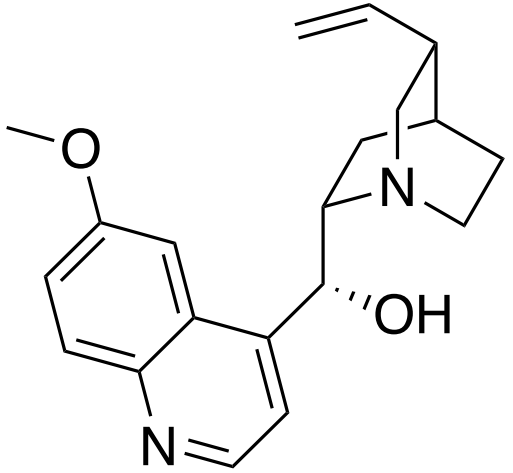
Used as an antimalarial for more than 300 years

1813 - First isolation reported

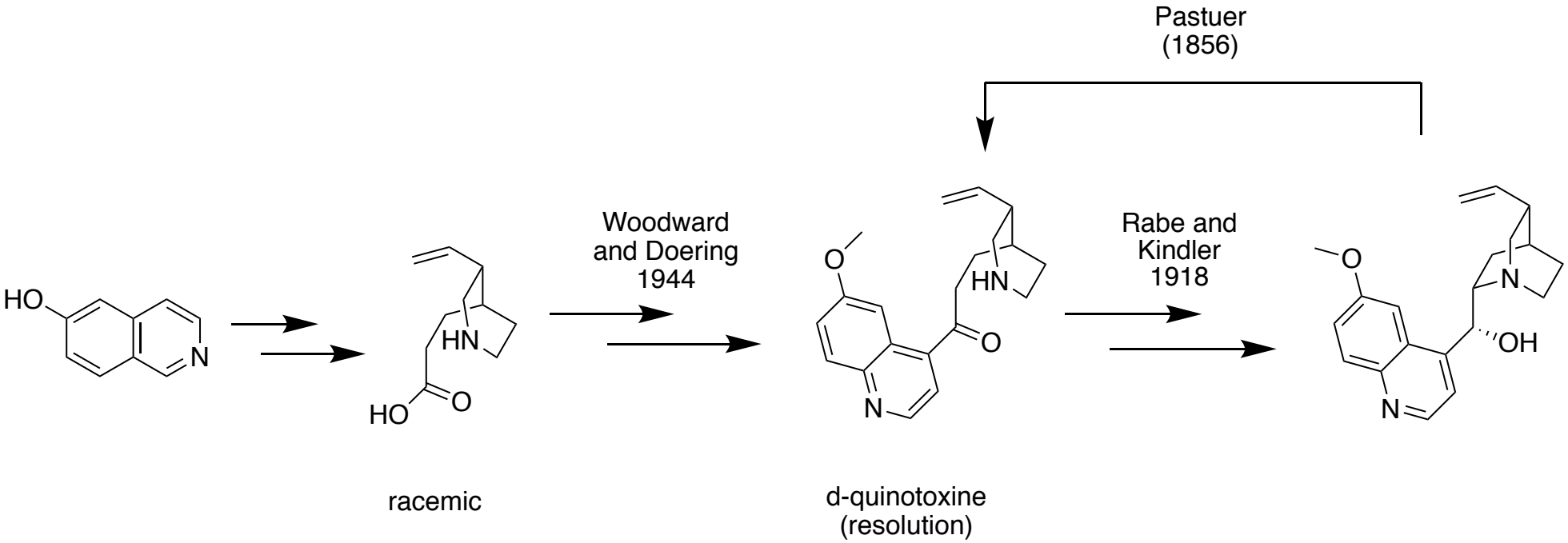
Atom connectivity established by Paul Rabe 1907 and synthesized from d-quinotoxine in 1918.

1944 - R.B. Woodward and W. Doering report a formal synthesis.

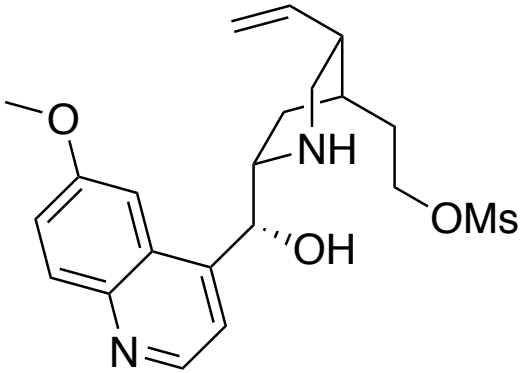
2001 - Gilbert Stork publishes first enantioselective synthesis.



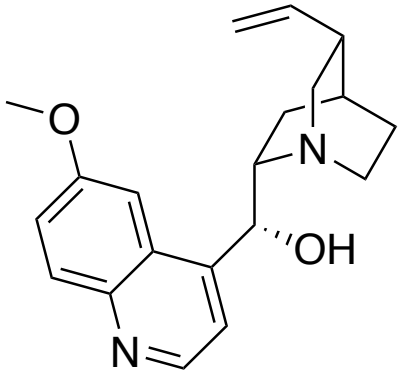
Early work

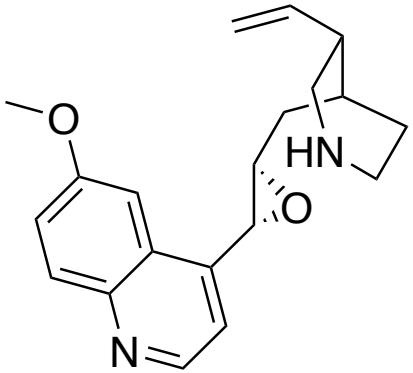

Pastuer
(1856)
HO
N
HN
HO
O
racemic
Woodward
and Doering
1944
O
HN
O
N
d-quinotoxine
(resolution)
Rabe and
Kindler
1918
O
N
OH
N

More recent Synthesis



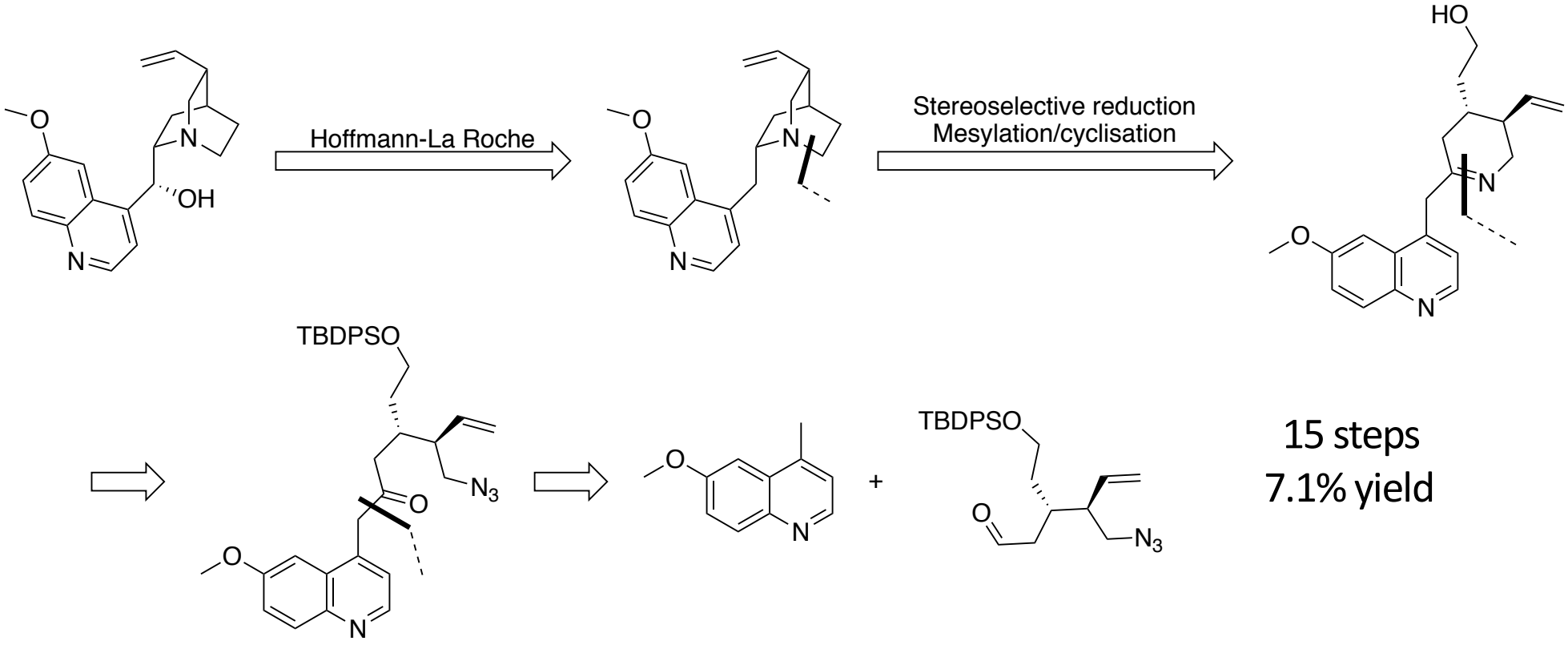
Stork (2001)





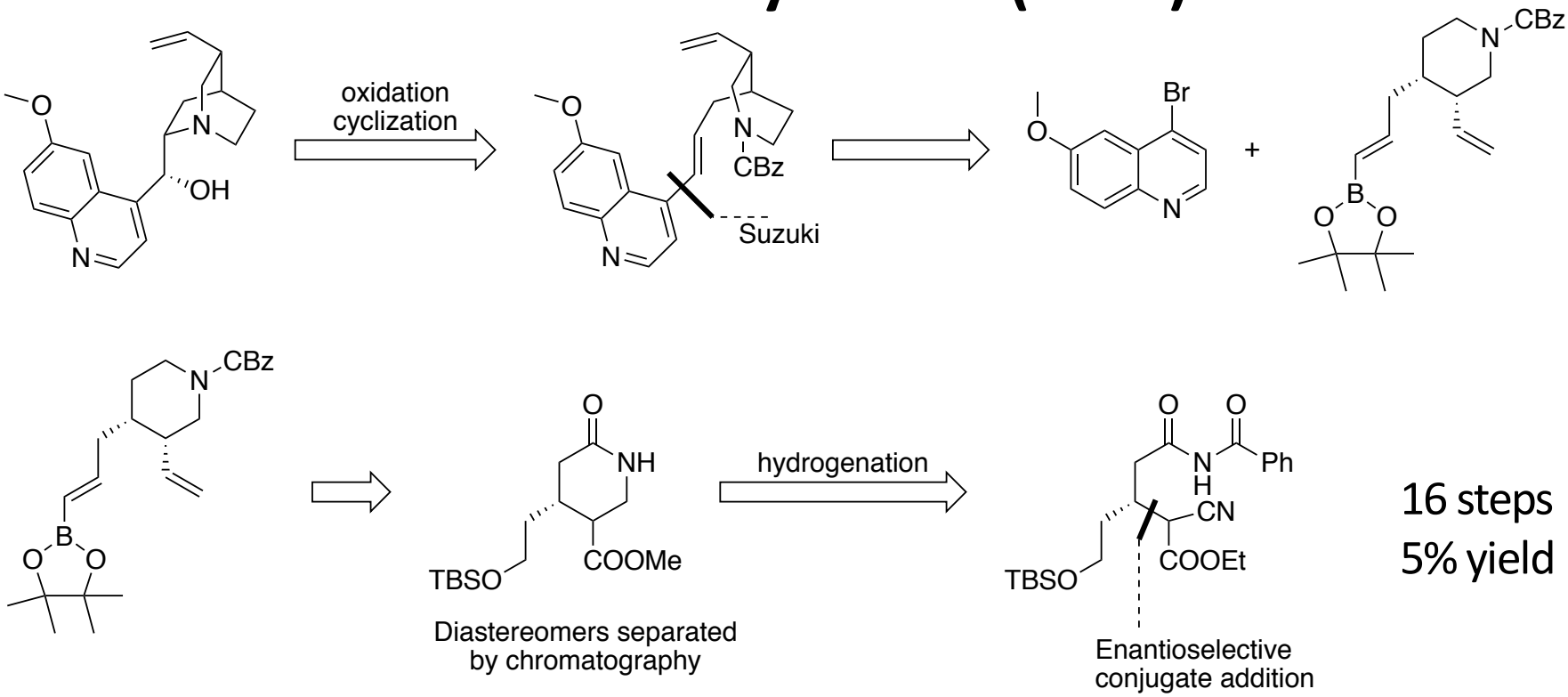
Uskokovic (1970,1978)
Jacobsen (2004)
Kobayashi (2004)
Aggarwal (2010)
Hatakeyama (2011)

Stork synthesis (2001)

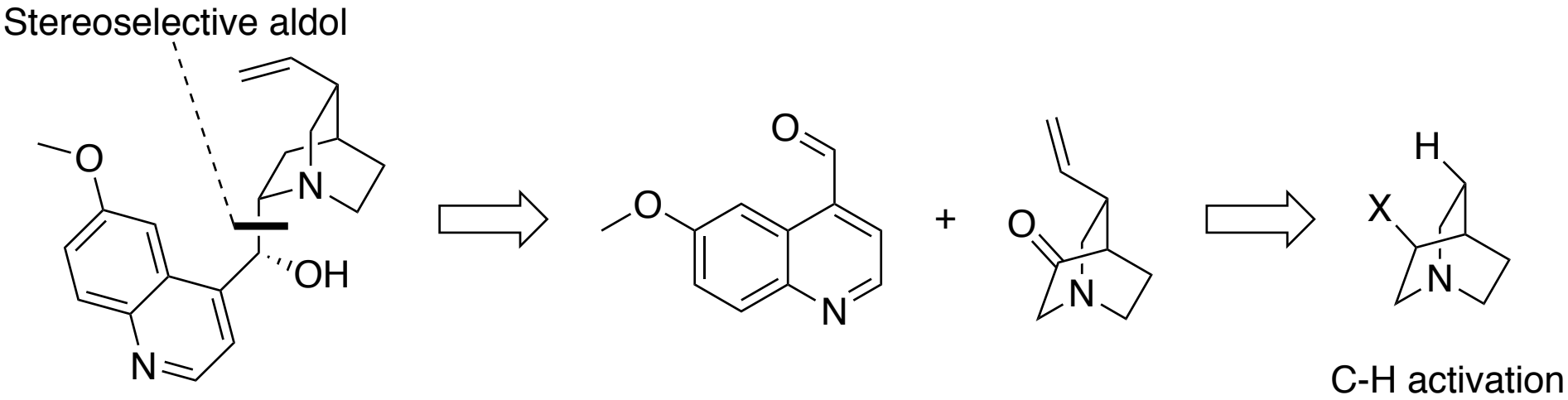


15 steps
7.1% yield

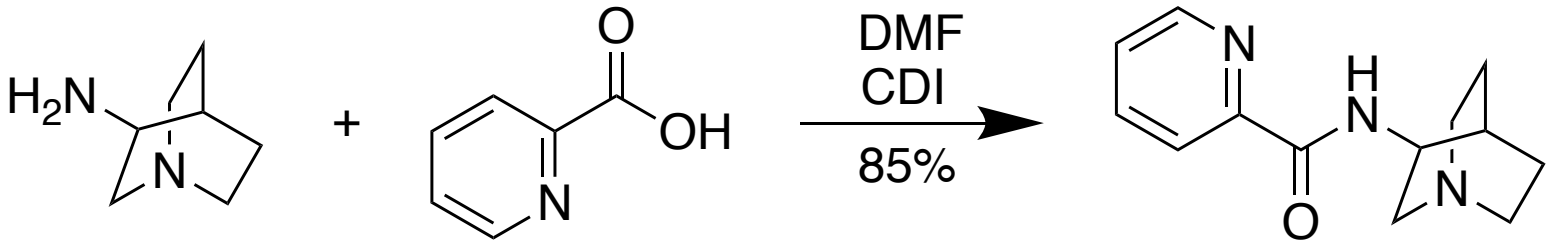
Jacobsen synthesis (2003)

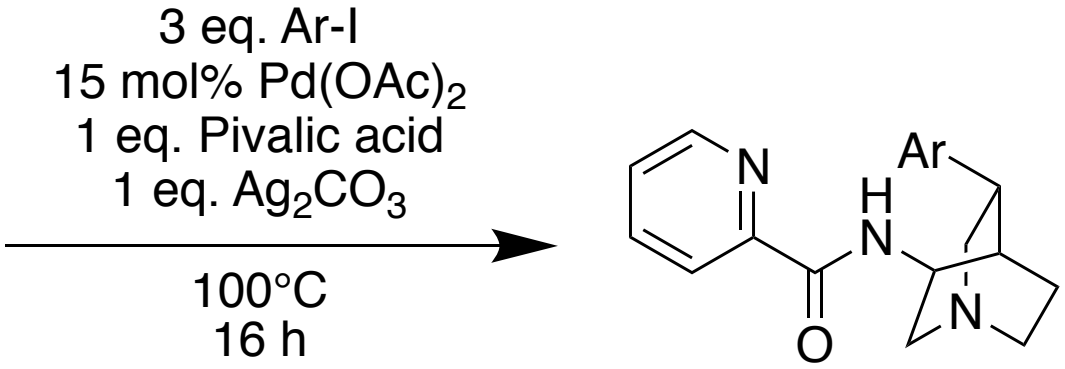


Title Paper: Retrosynthesis

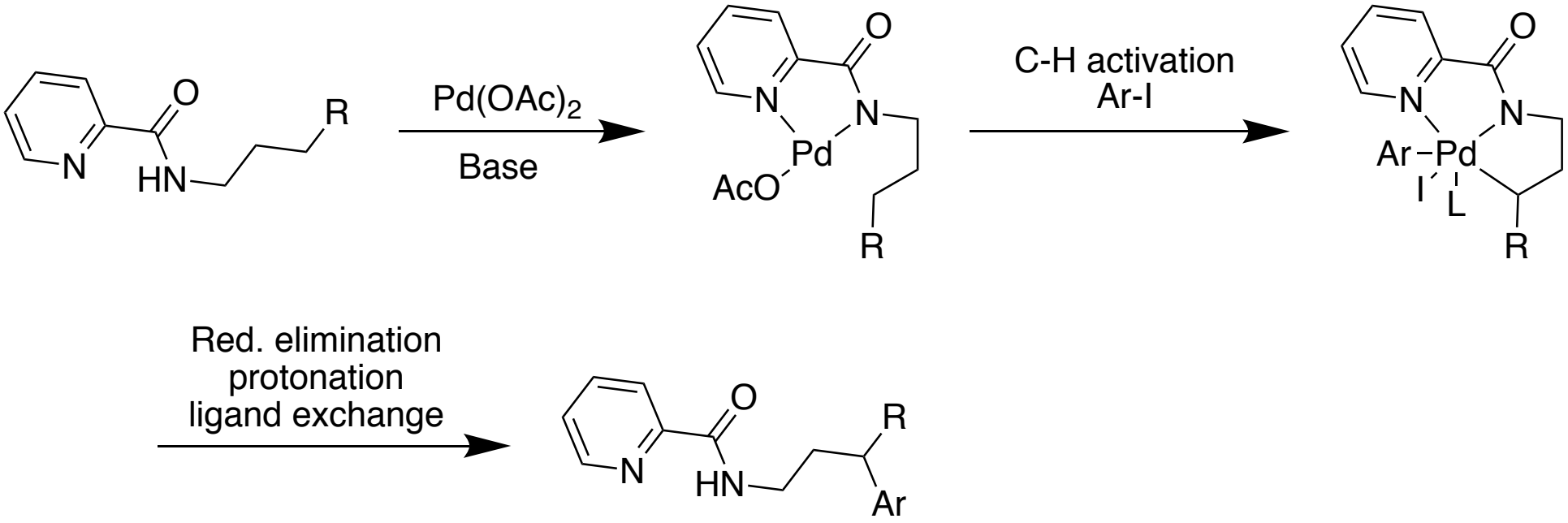


C-H activation



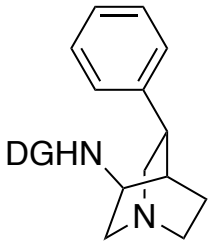


C-H activation mechanism

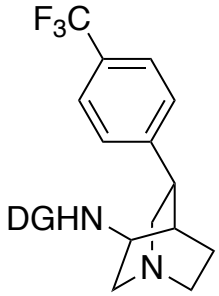


O. Daugulis et al., *J. Am. Chem. Soc.* 2005, **127**, 13154-13155

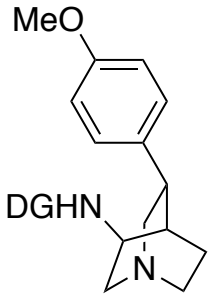
Scope



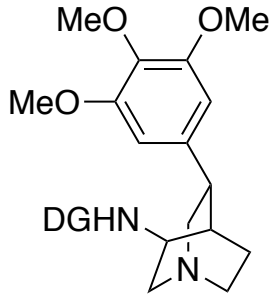
90%



88%



94%



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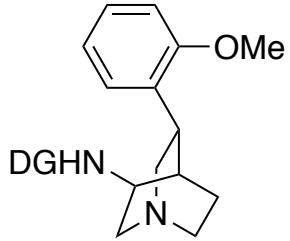
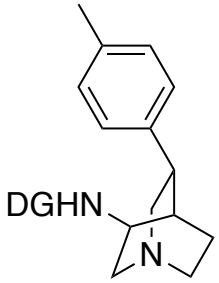
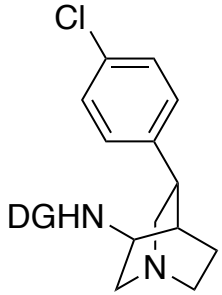


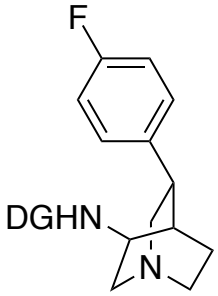
49%



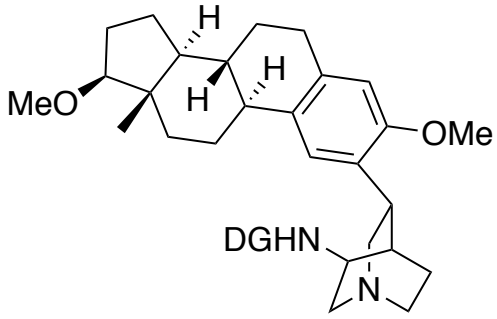
84%



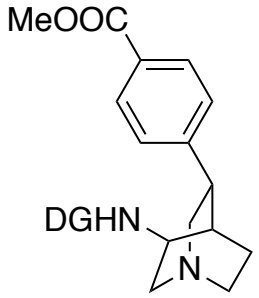
79%



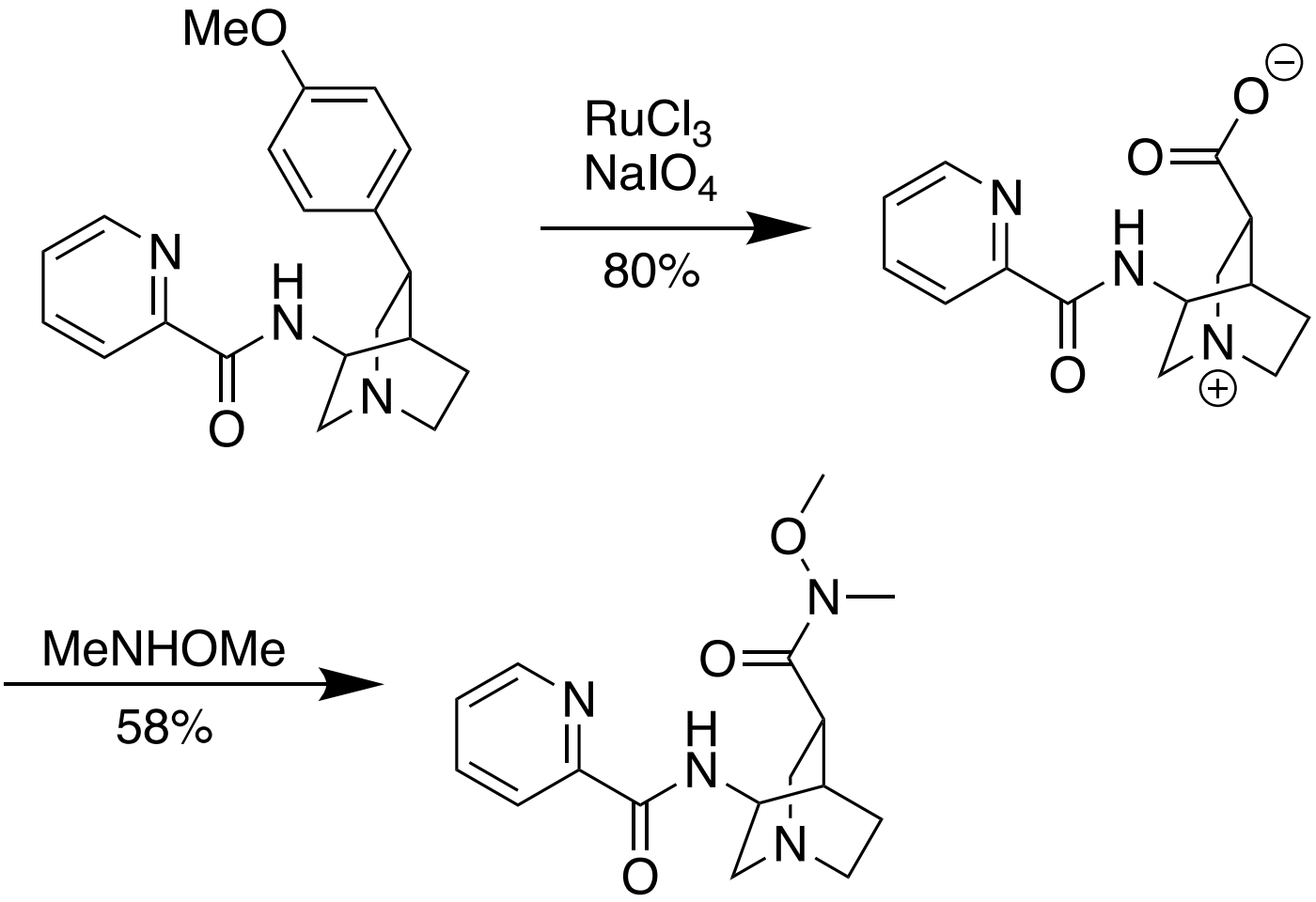
43%

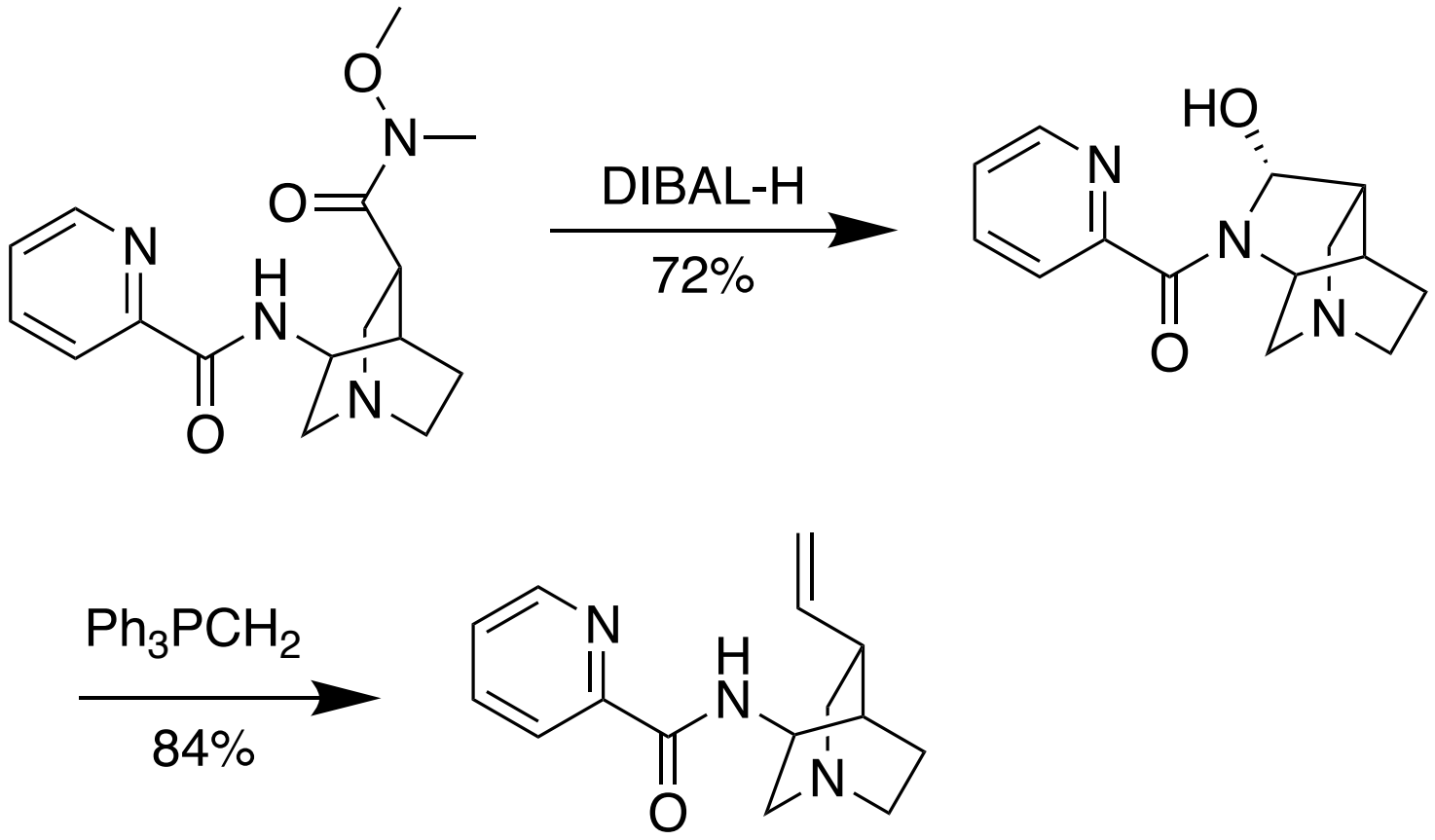


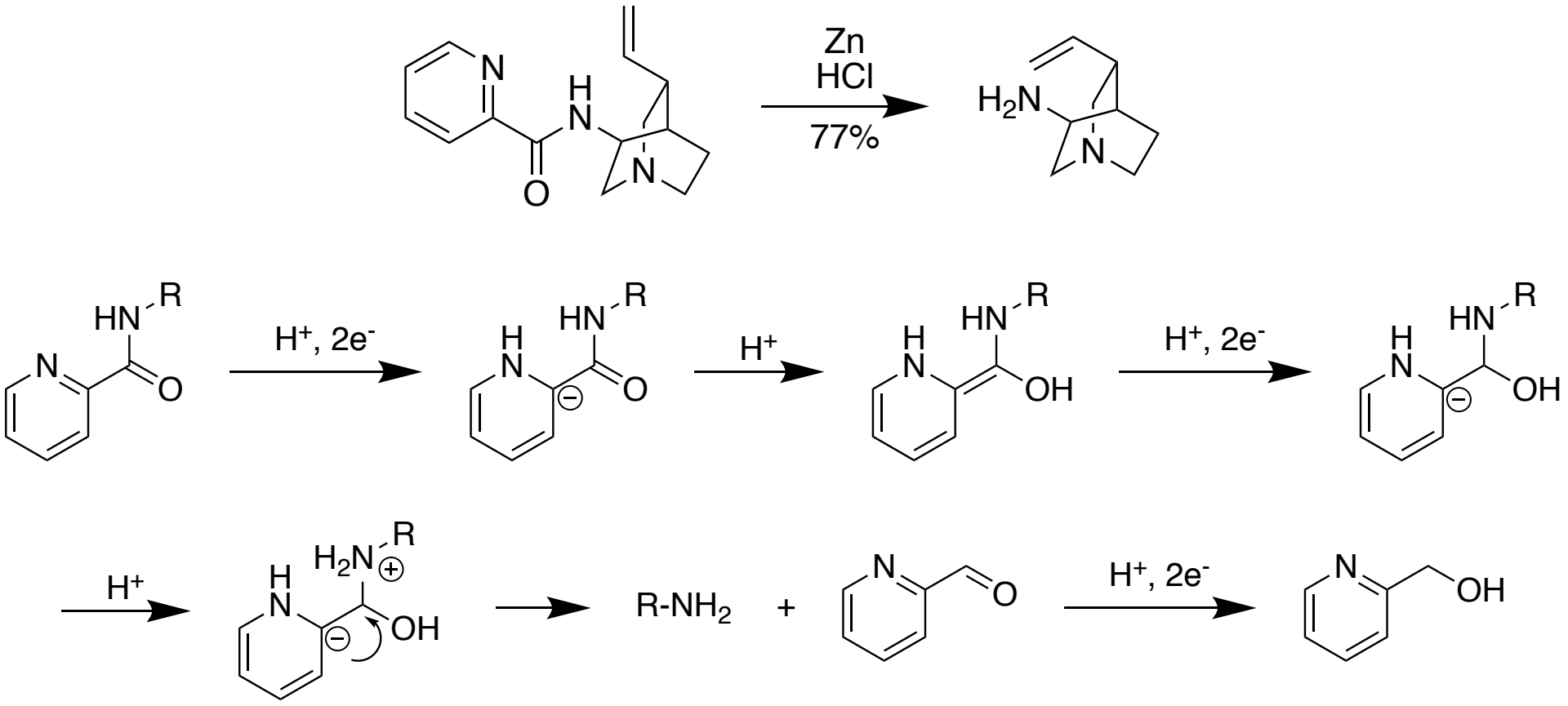
26%



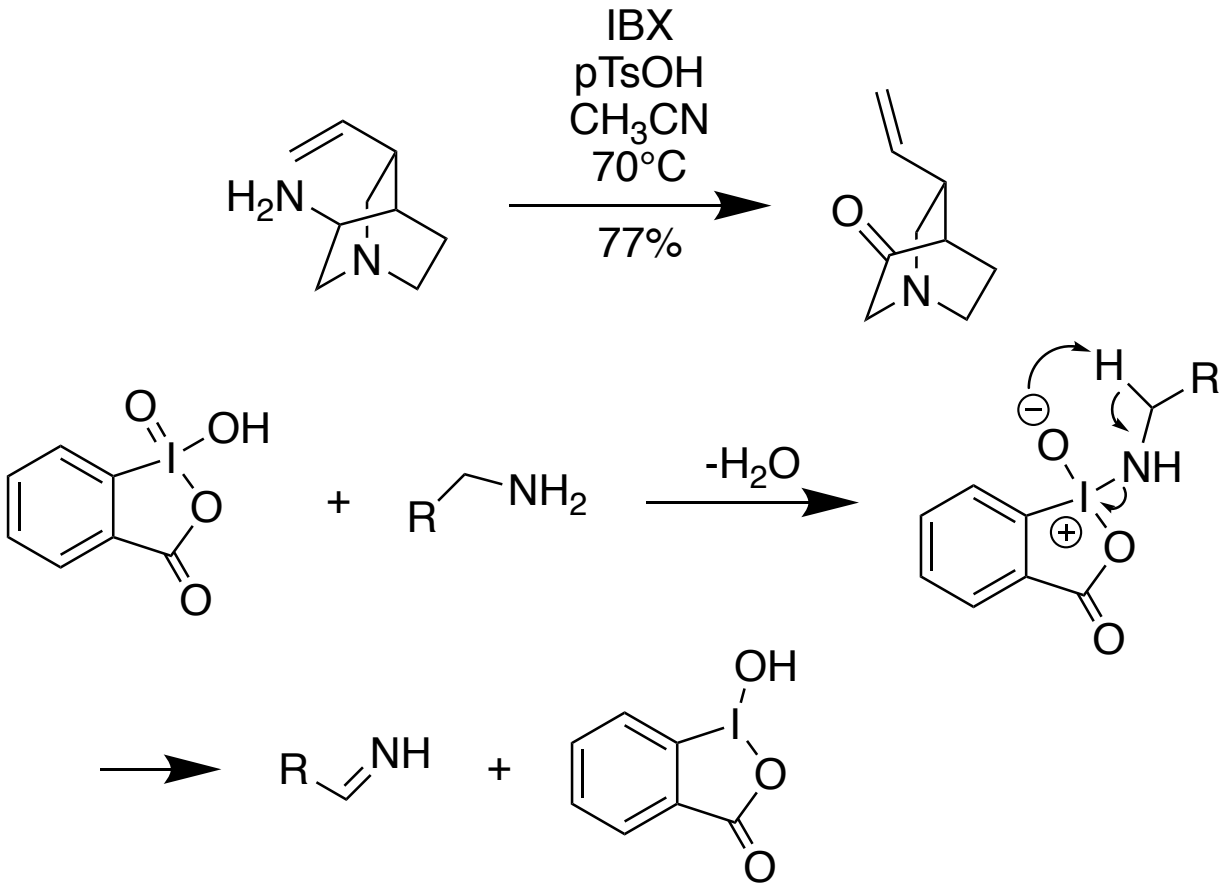
57%


MeO
N
H
N
O
N
RuCl3
NaIO4
80%
O
O
N
H
N
O
N
MeNHOMe
58%
O
N
O
N
H
N
O
N


O
N
O
N
H
N
O
DIBAL-H
72%
HO
N
N
O
N
Ph3PCH2
84%
N
H
N
O
N

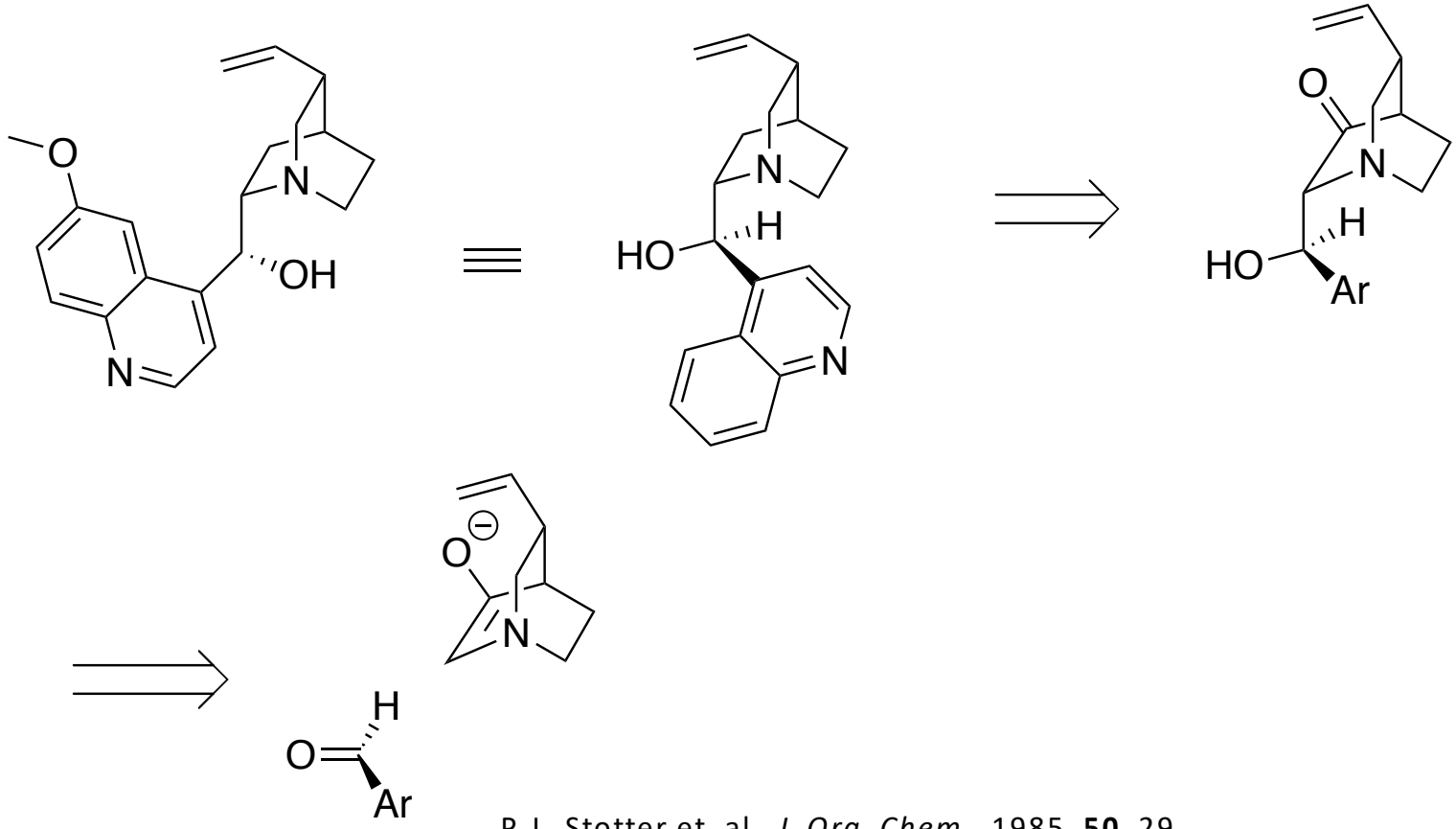


D. H. O'. Donovan et. al., *Tet. Lett.*, , **57**, 2962–2964



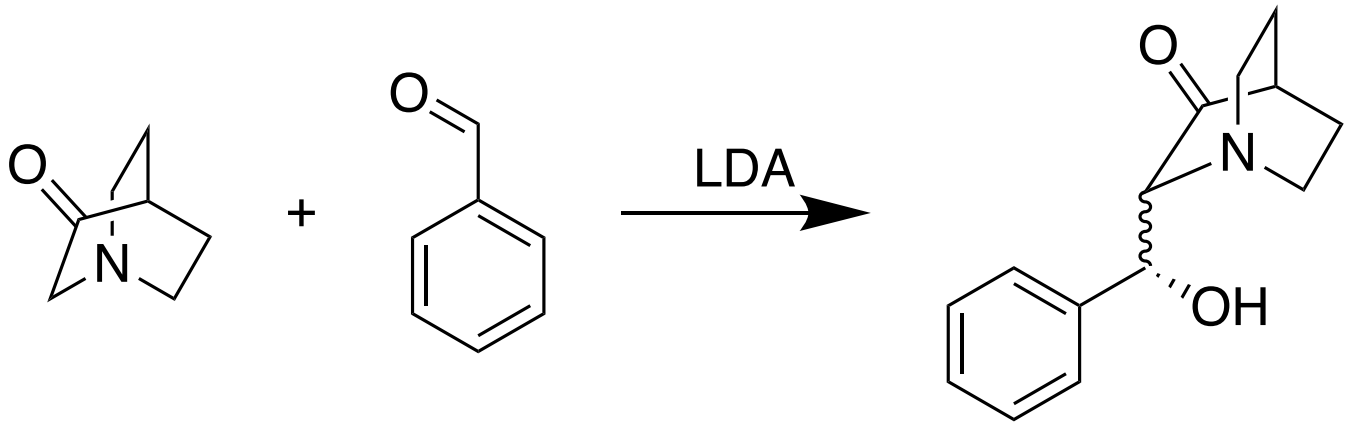
K. C. Nicolaou et. al., *Angew. Chem. Int. Ed.,* 2003, **42**, 4077

Aldol reaction – model studies



P. L. Stotter et. al., *J. Org. Chem*., 1985, **50**, 29

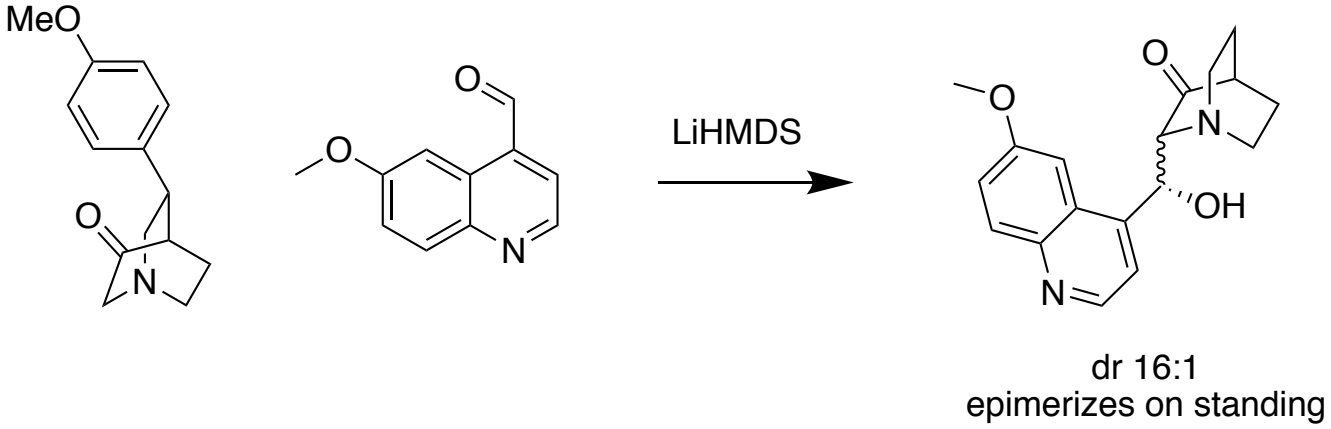
Aldol reaction – model studies



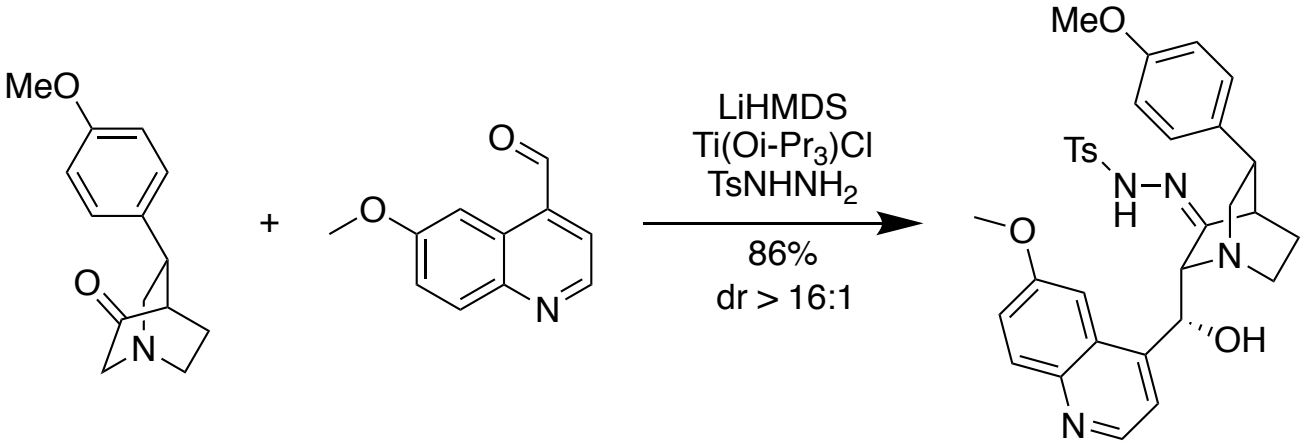
about 90% stereoselectivity
based on crude NMR

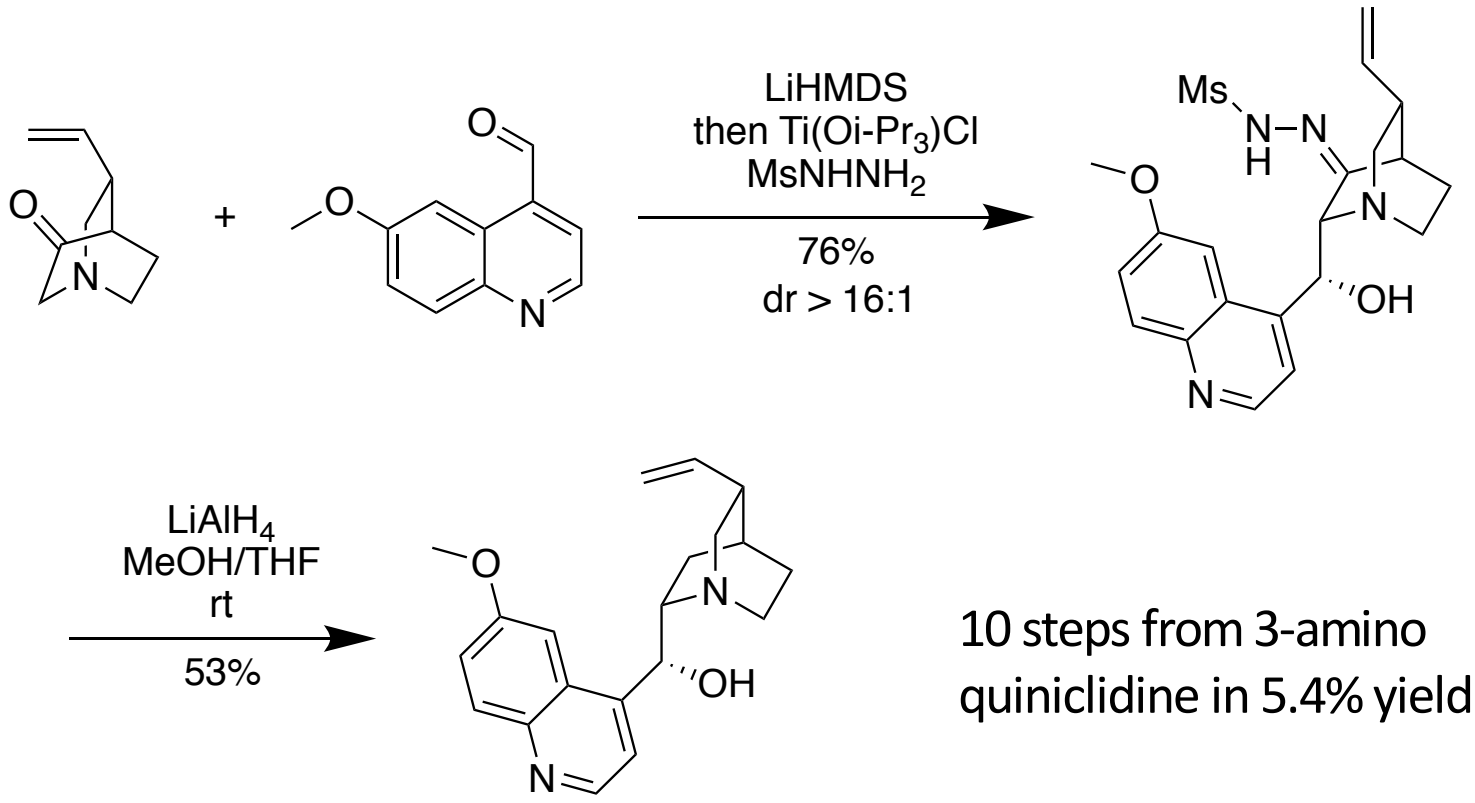
epimerization in solution very fast
1:1 mixture after 48 h in $CDCl_3$

P. L. Stotter et. al., *J. Org. Chem*., 1985, **50**, 29



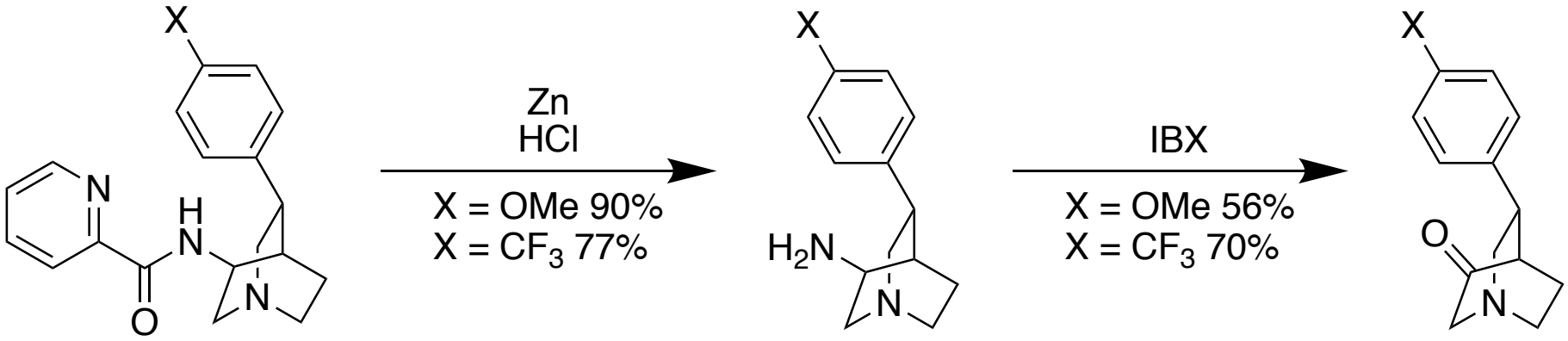
dr 16:1
epimerizes on standing

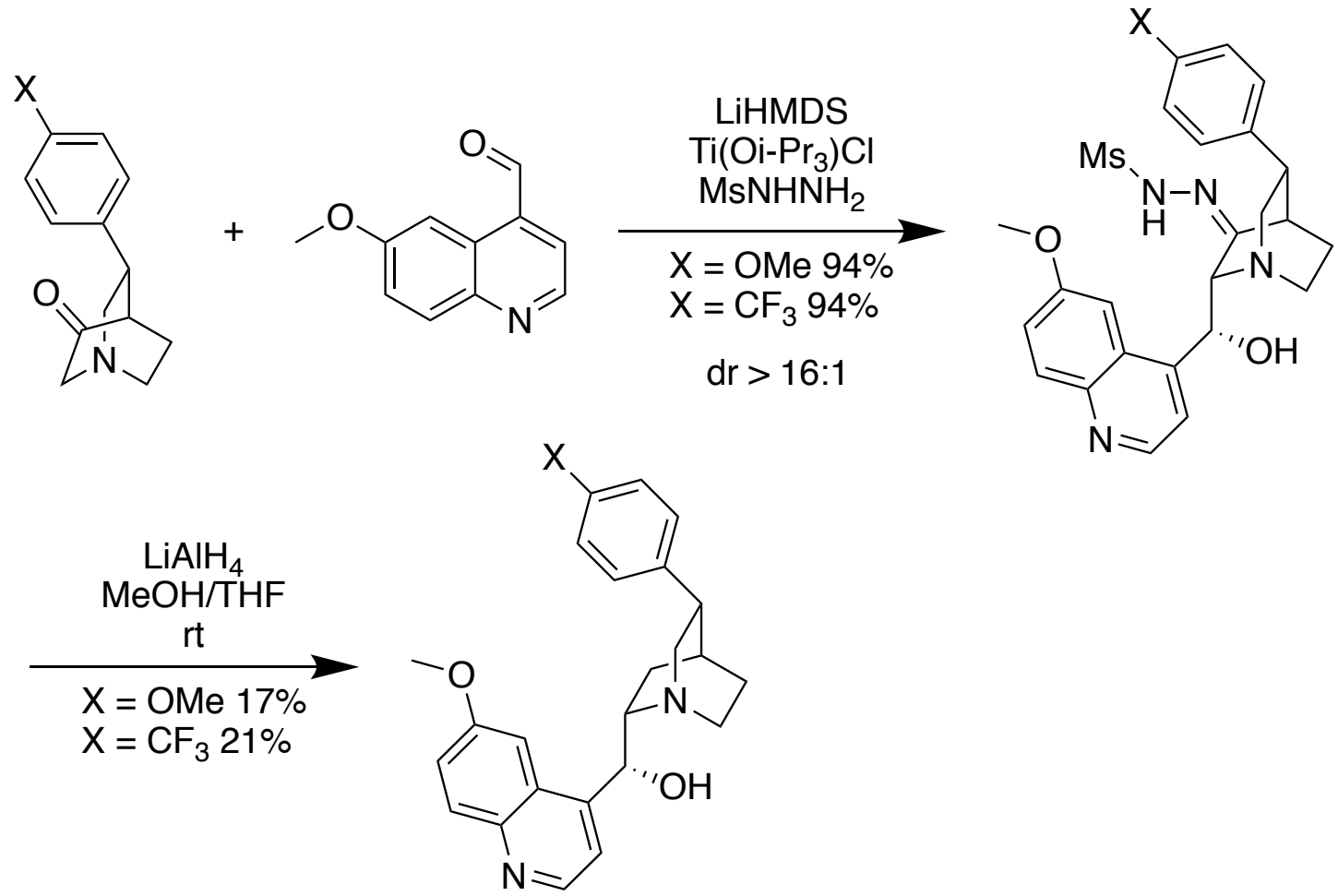




10 steps from 3-amino quiniclidine in 5.4% yield

C-3 analogues



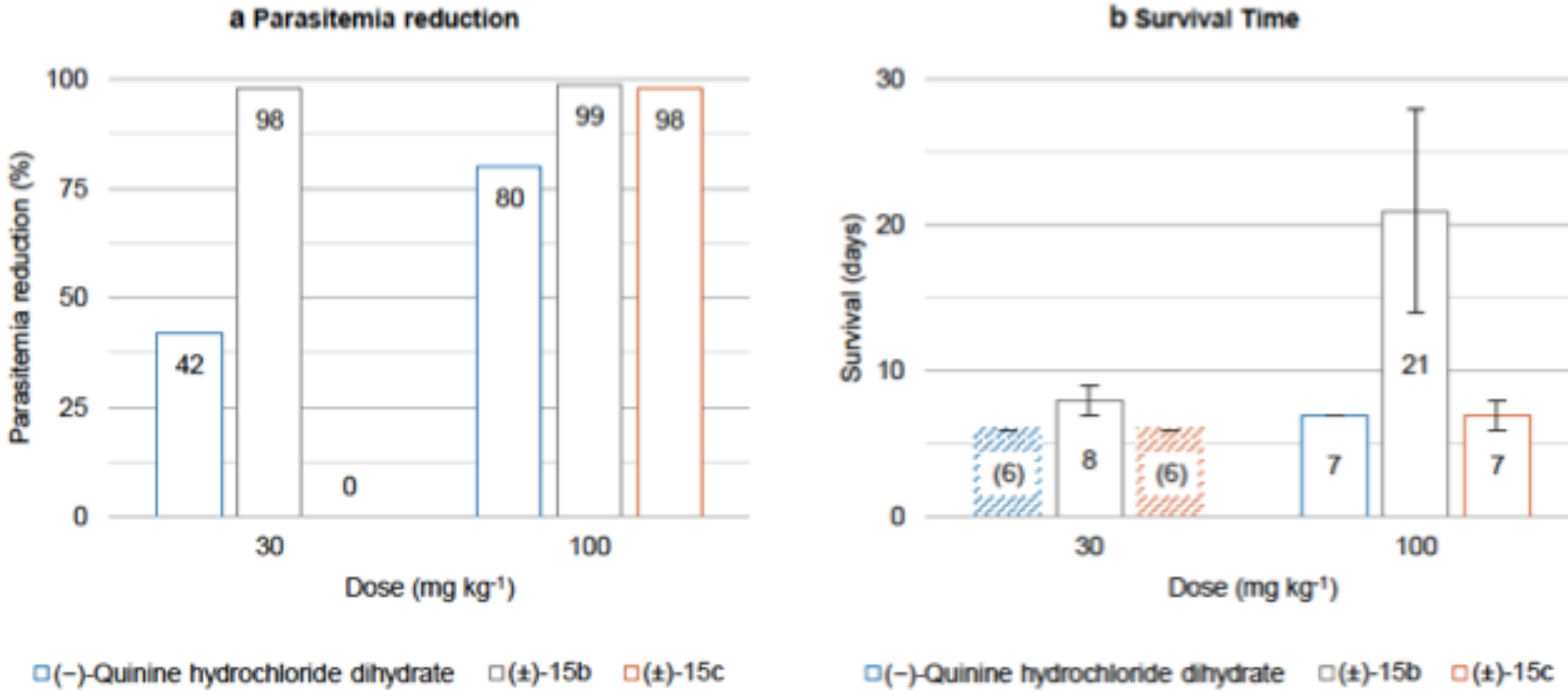

X
O
N
+
O
O
N
LiHMDS
Ti(Oi-Pr3)Cl
MsNHNH2
X = OMe 94%
X = CF3 94%
dr > 16:1
X
Ms
N–N
H
O
N
OH
N
LiAlH4
MeOH/THF
rt
X = OMe 17%
X = CF3 21%
X
O
N
OH
N

In-vitro antiprotozoal activity

Substance	IC_{50} against *P. falciparum* (strain NF54) (nM)[a]	IC_{50} for cytotoxicity (strain L6) (μM)[a]
Chloroquine	6 ± 3[b]	—
Podophyllotoxine	—	0.010 ± 0.002[b]
(−)-Quinine (**1**)	22 ± 3[b]	111 ± 21[c]
(+)-Quinine (**1**)	122 ± 3[b]	142 ± 21[c]
(±)-**15b**	5 ± 5[b]	7 ± 3[b]
(±)-**15c**	12 ± 15[b]	16 ± 2[b]

[a] The values are given as mean ± standard deviation. [b] 3 replicates. [c] 2 replicates.

In-vivo screening against P. berghei



Summary

Total synthesis of both enantiomers of Quinine accomplished in 10 steps in 5.4% overall yield from 3-aminoquininclidine using a stereoselective aldol reaction.

C-H activation enables access to novel analogues with improved in-vitro and in-vivo potency in only 6 steps from aminoquiniclidine