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Enantioselective Total Synthesis of (−)-Arcutinine

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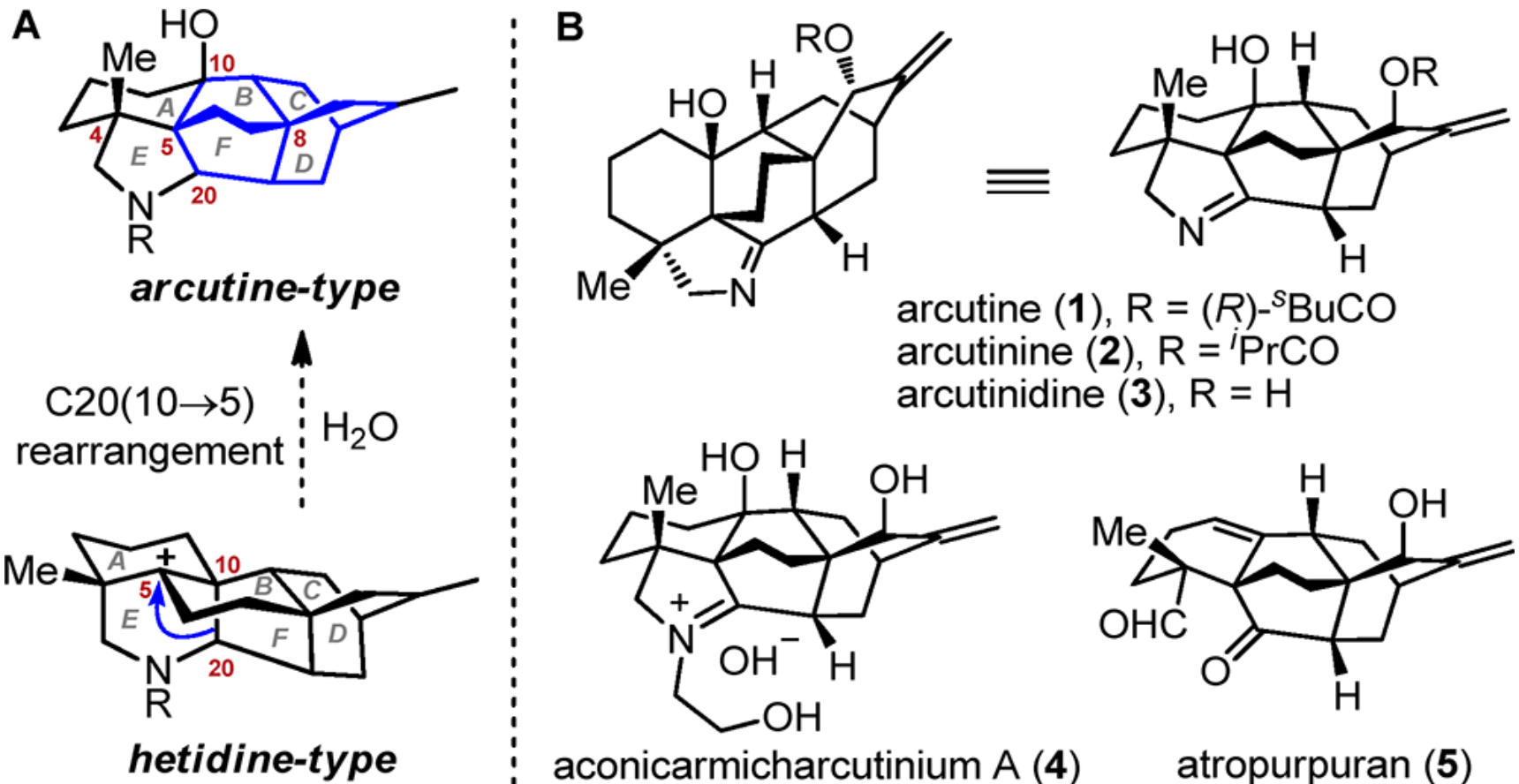
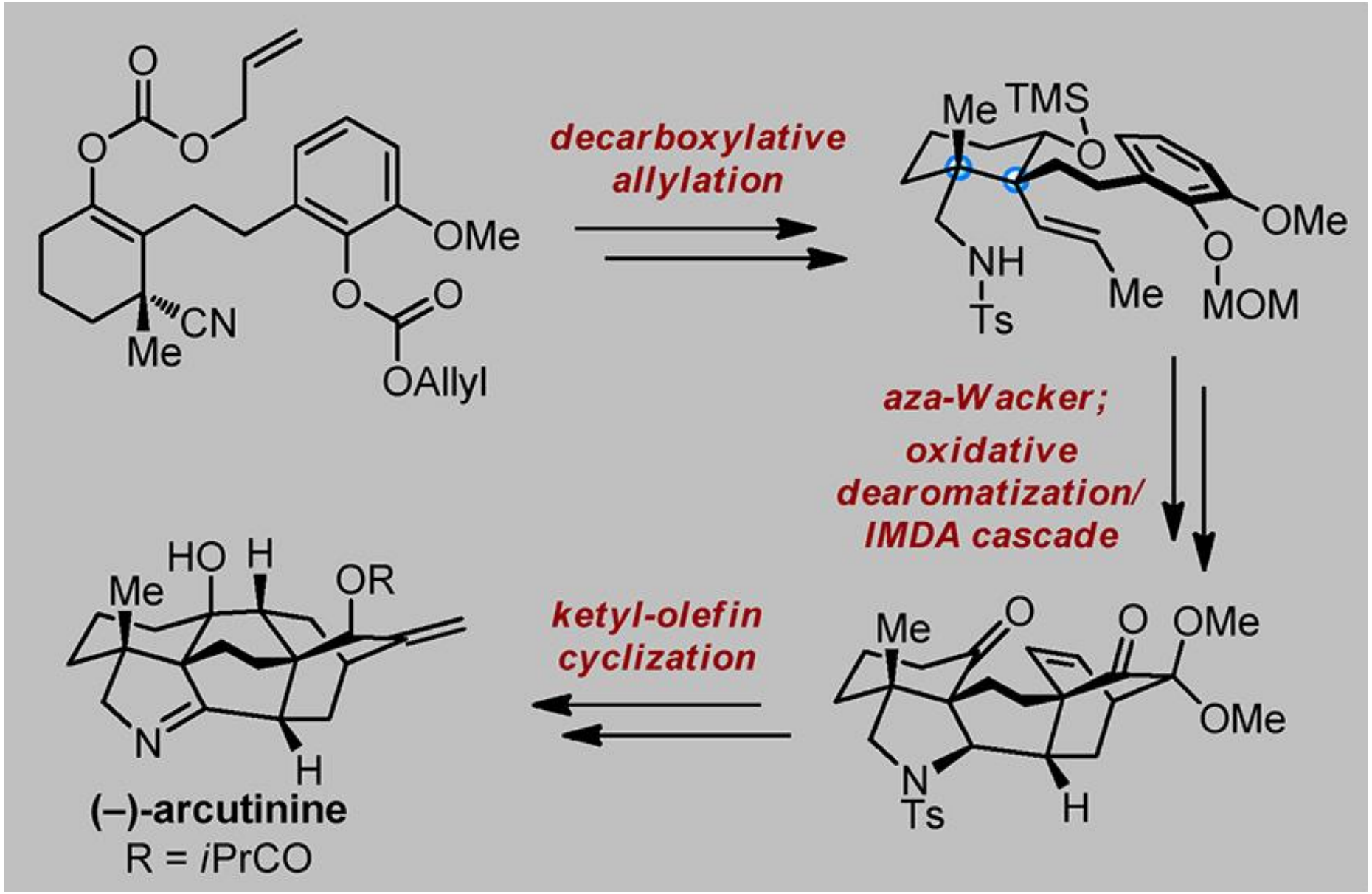
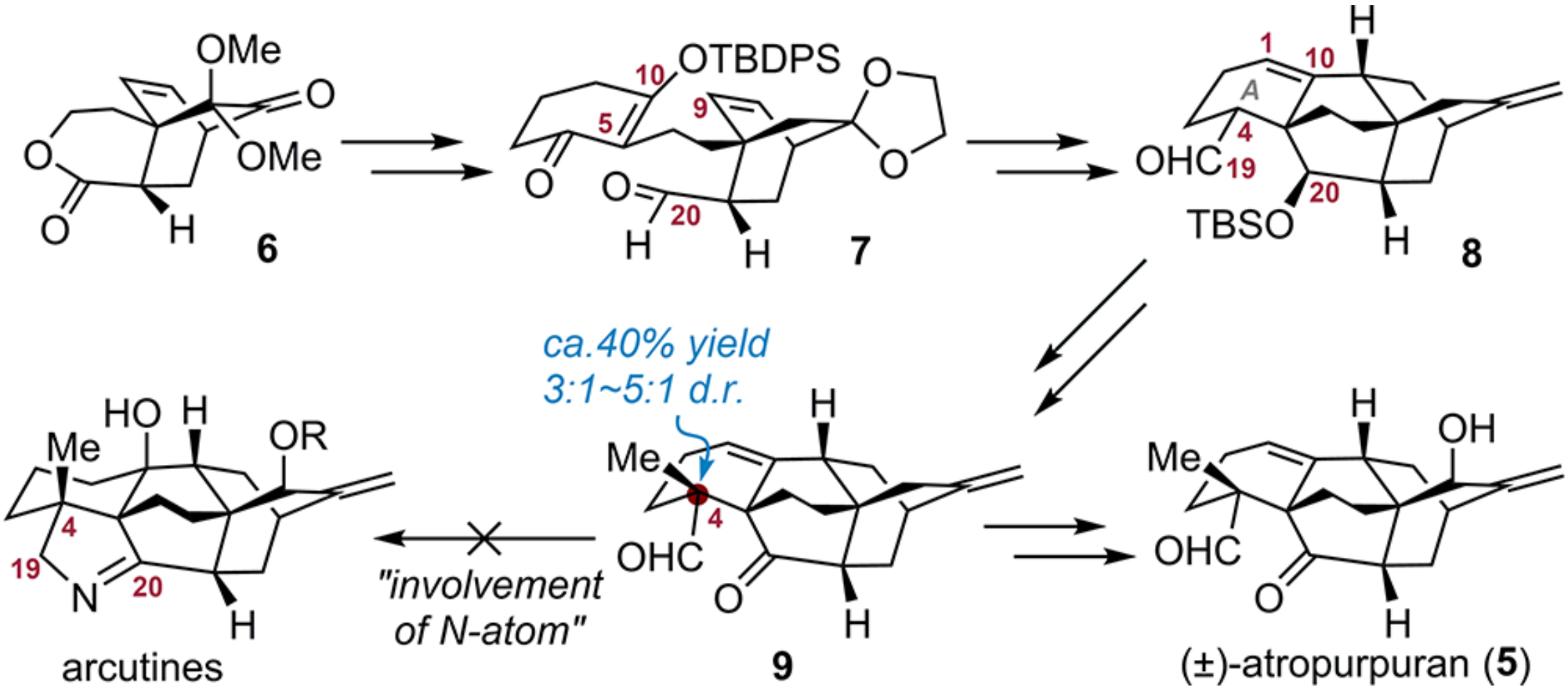


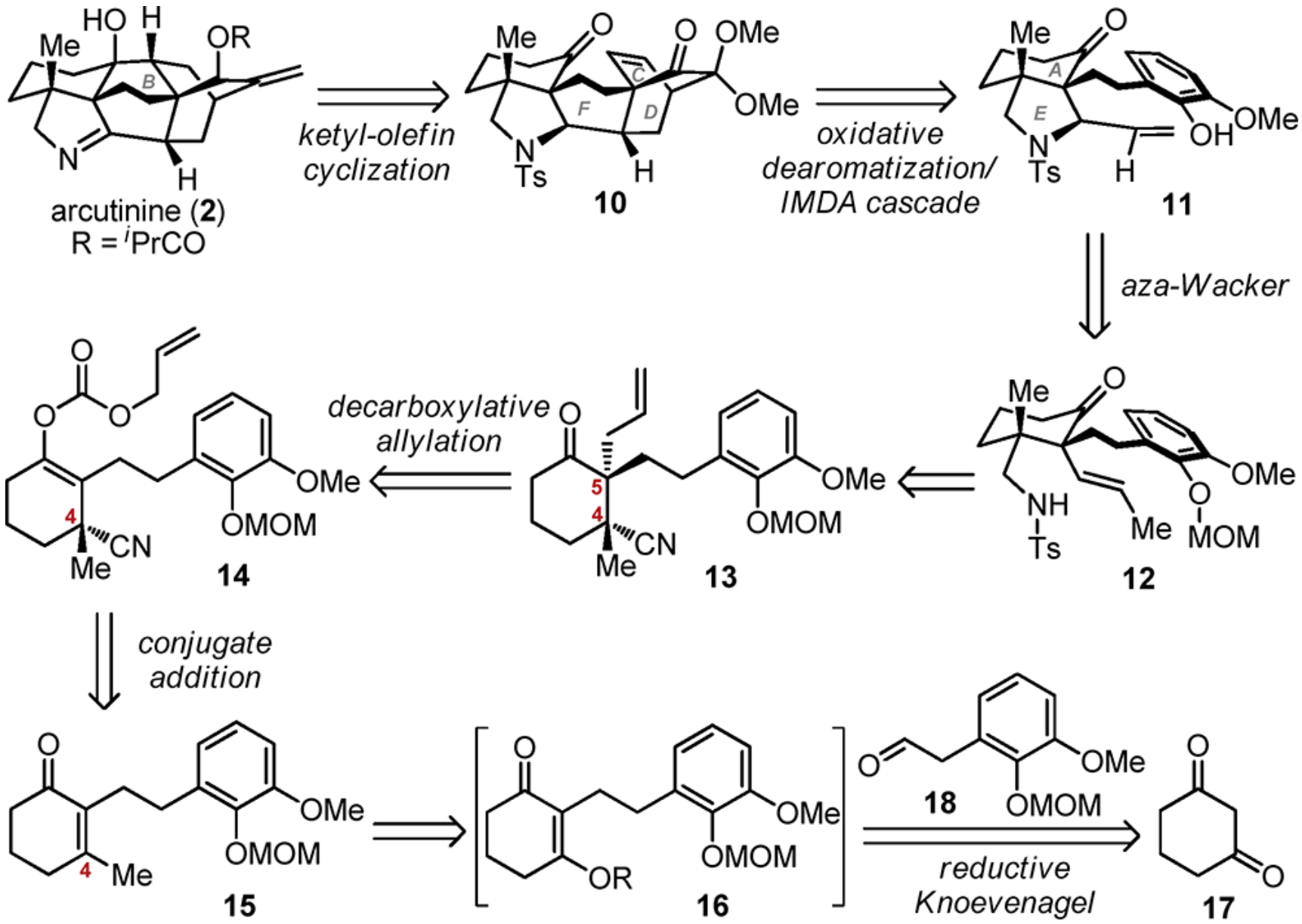

decarboxylative allylation
aza-Wacker; oxidative dearomatization/ IMDA cascade
ketyl-olefin cyclization
(–)-arcutinine
R = iPrCO

Scheme 1. Our Previous Synthesis of (±)-Atropurpuran (5) and Attempted Access to the Arcutines

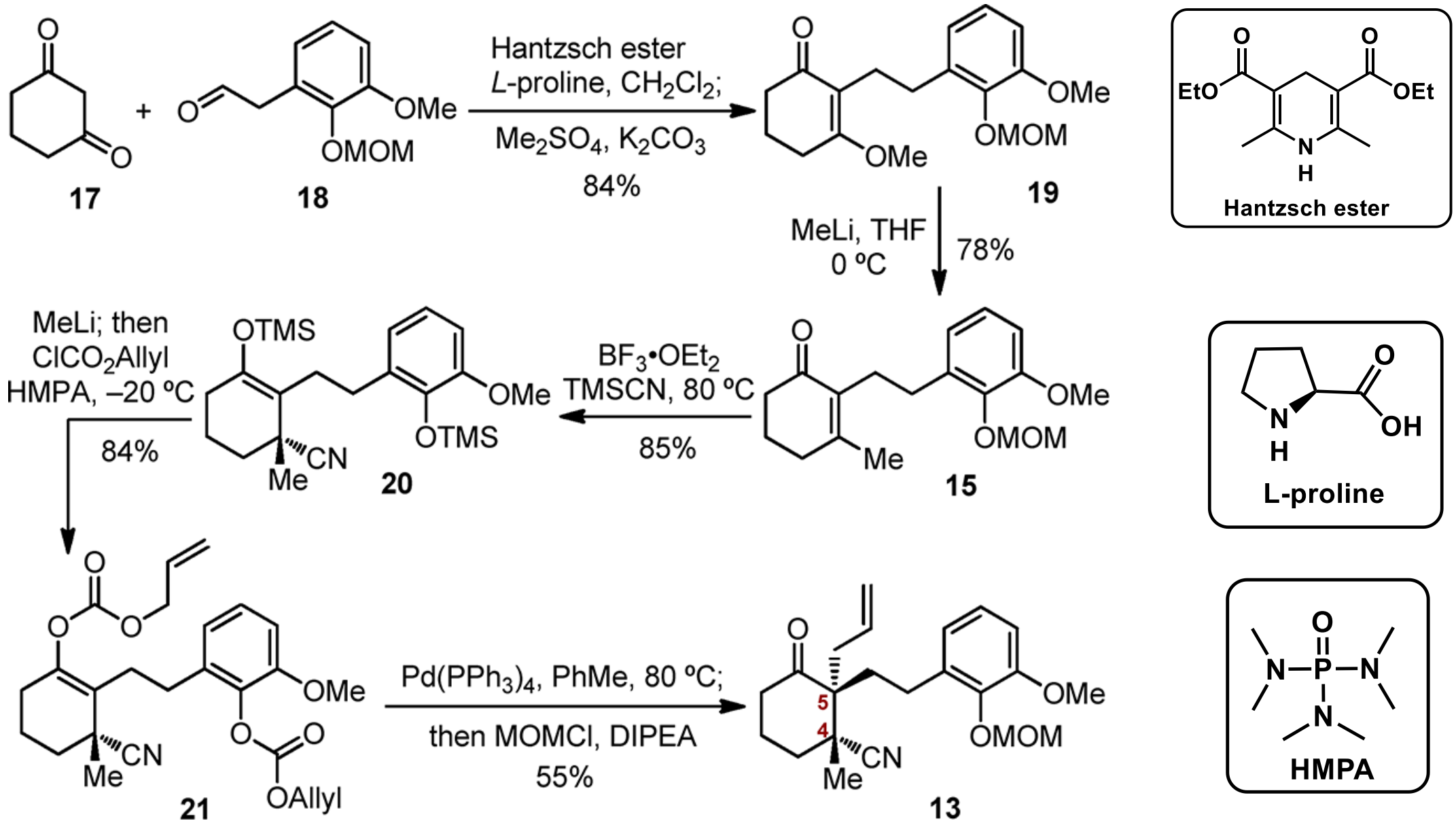


DOI: 10.1038/ncomms12183

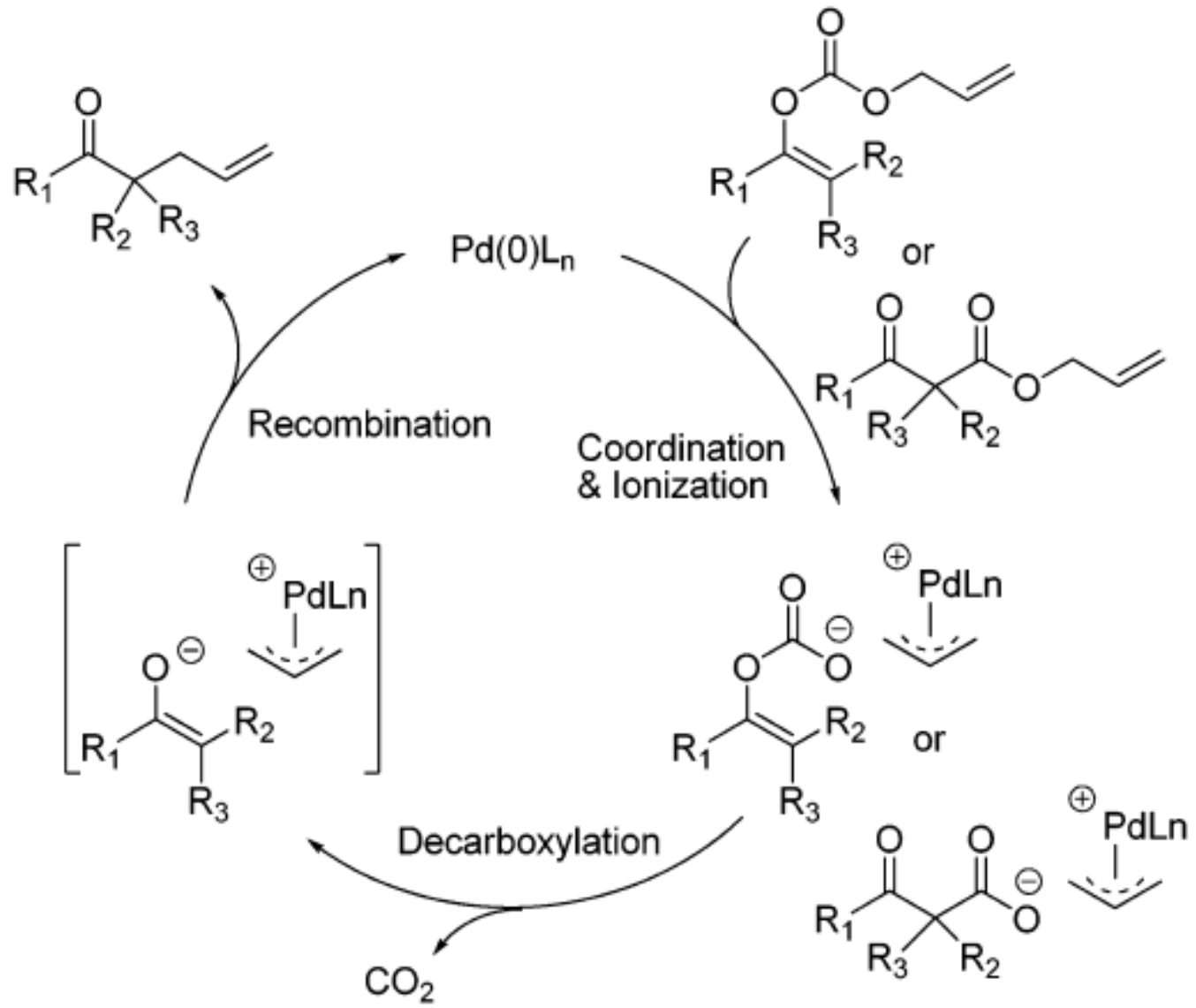
Scheme 2. Retrosynthetic Analysis of Arcutinine (2)



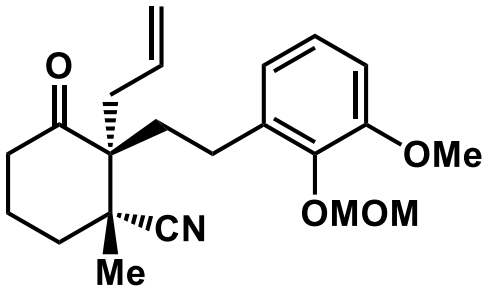
Scheme 3. Preparation of the Key Intermediate 13 with C4 and C5 Vicinal Quaternary Stereogenic Centers



Mechanism of Palladium-Catalyzed Decarboxylative Allylic Alkylation



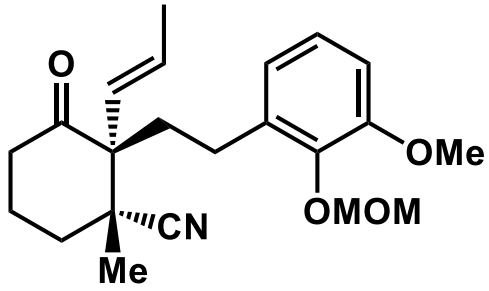
Scheme 4. Synthesis of the Key Intermediate 10



13

$PdCl_2(MeCN)_2$
PhMe, 110℃

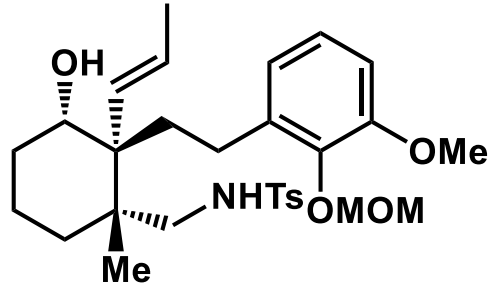
then MOMCl
DIPEA, 75%



22

1) $LiAlH_4$, 50℃
2)TsCl, Et_3N, 0℃

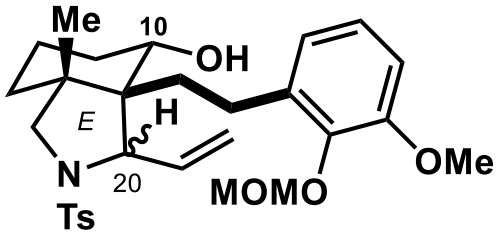
84% two steps



23

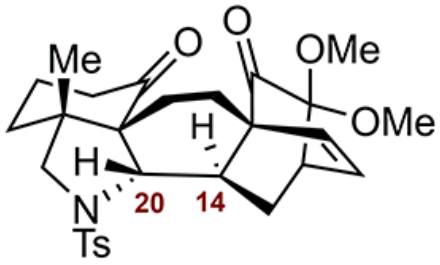
$Pd(OAc)_2$, DAF
PhMe, O_2, 50℃

82%, 1:1.5 *d.r.*



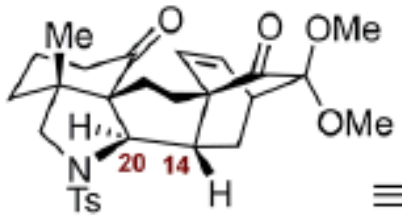
24a/b (inseparable)

1) DMP, $NaHCO_3$
2) TFA, DCM
3) $PhI(OAc)_2$, MeOH, reflux



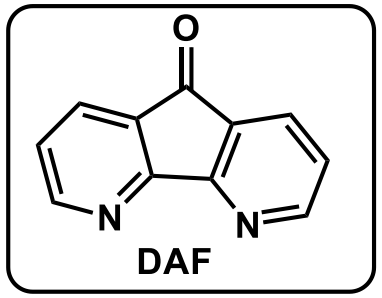
25 (39% from 24a/b)

+



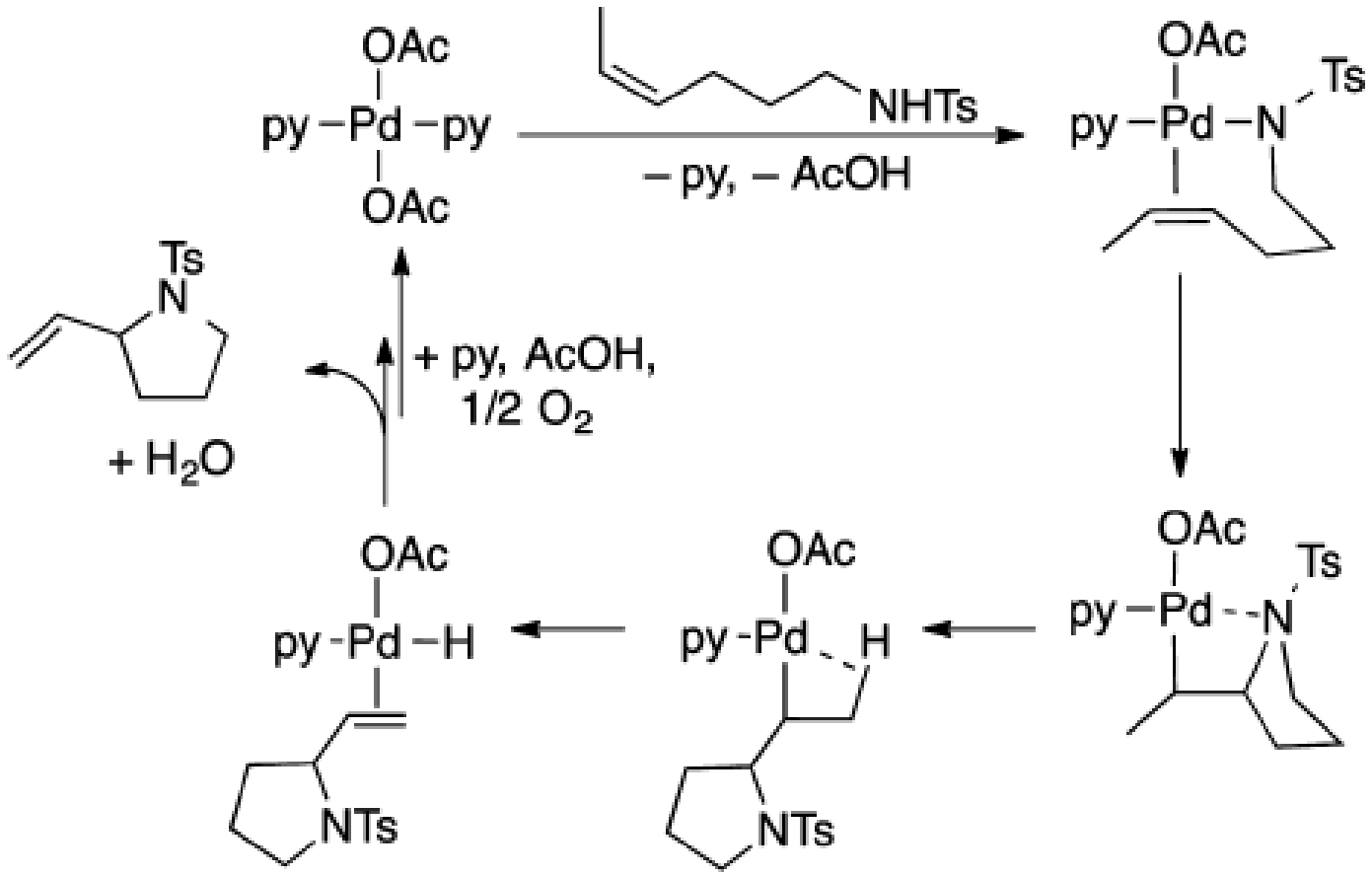
≡

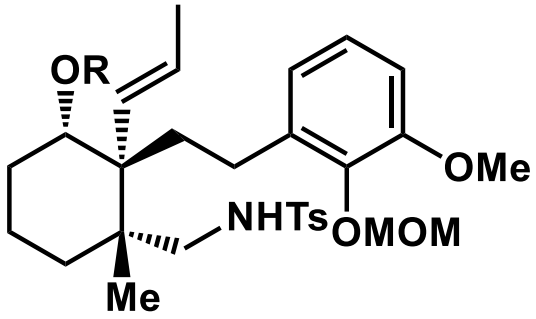
10 (25% from **24a/b**)
[X-ray]



DAF

Mechanism of $Pd(OAc)_2$/Pyridine-Catalyzed Aza-Wacker Cyclization

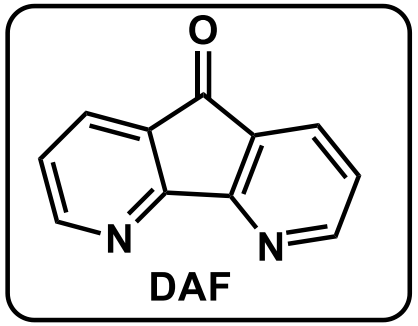


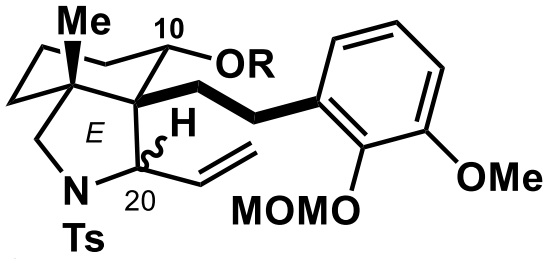


26, R=TMS
27, R=TBS

$Pd(OAc)_2$, DAF
PhMe, O_2, 50℃

82%, 1:1.5 *d.r.*

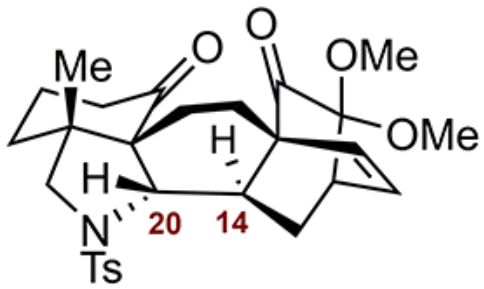




1)TBAF, 0℃
2)DMP, $NaHCO_3$
3)TFA, DCM
4)$PhI(OAc)_2$
MeOH, reflux

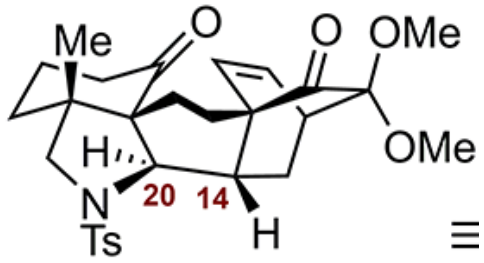
R = TMS (2.5:1 *d.r.*)
- **28a** (α-H20, 54% from **26**)
- **28b** (β-H20, 22% from **26**)

R = TBS (3:1 *d.r.*)
- **29a** (α-H20, 56% from **27**)
- **29b** (β-H20, 18% from **27**)



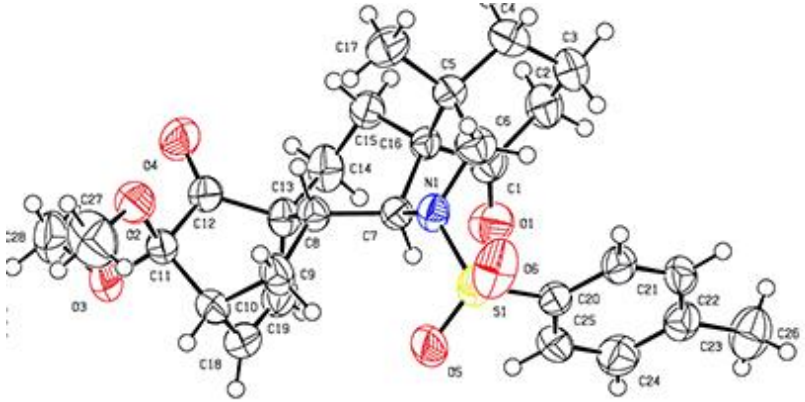
25 (61% overall from 28b)

+



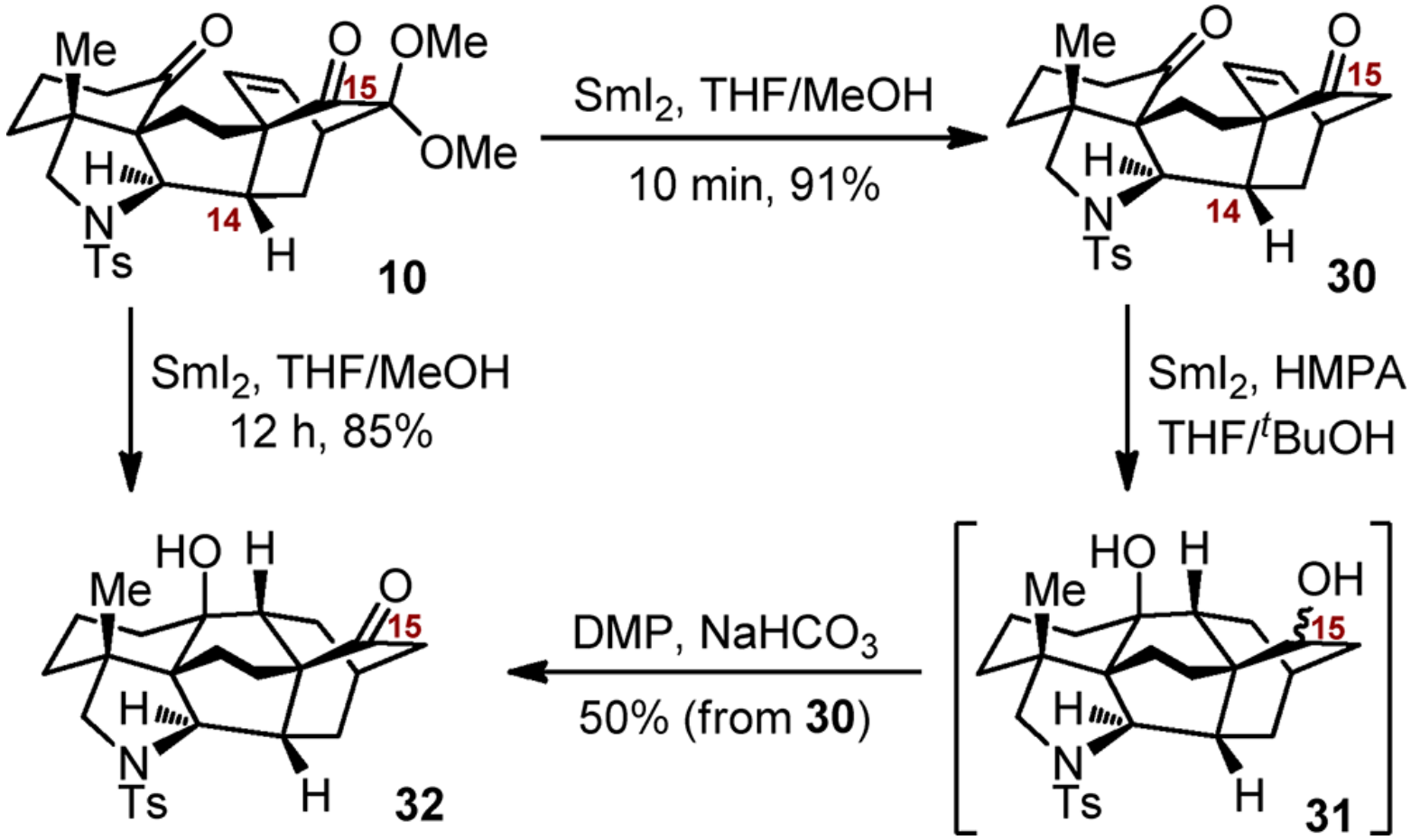
≡

10 (59% overall from 28a)

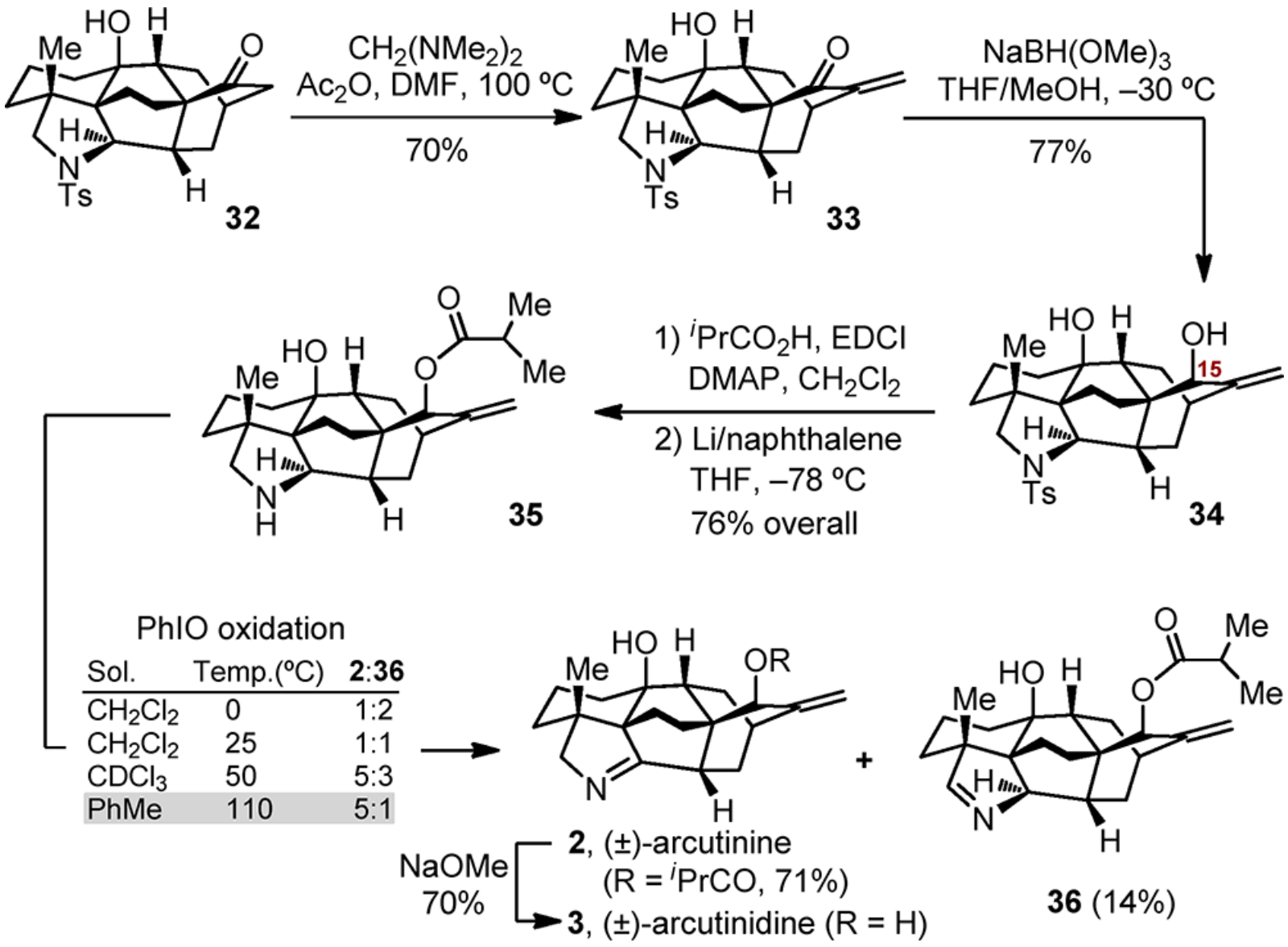


ORTEP of (±)-**10**

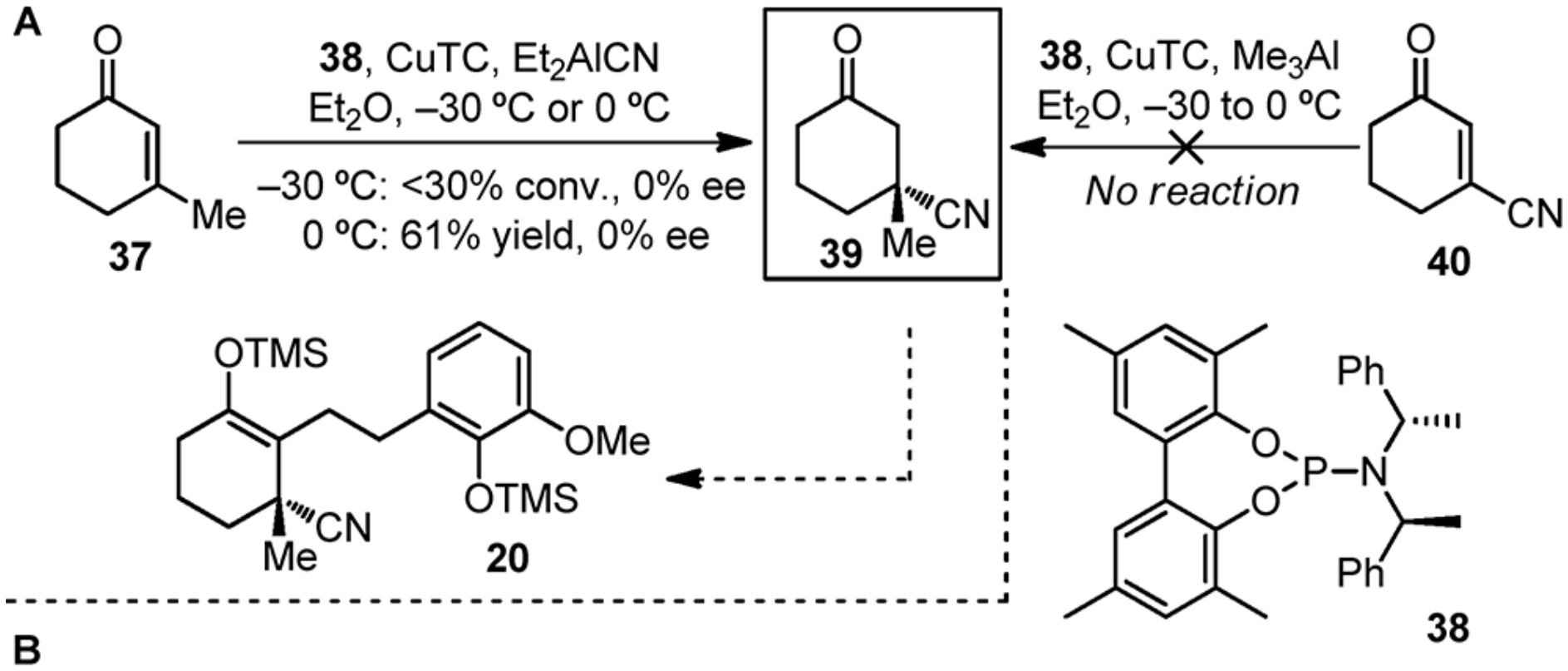
Scheme 5. Construction of the Hexacyclic Core



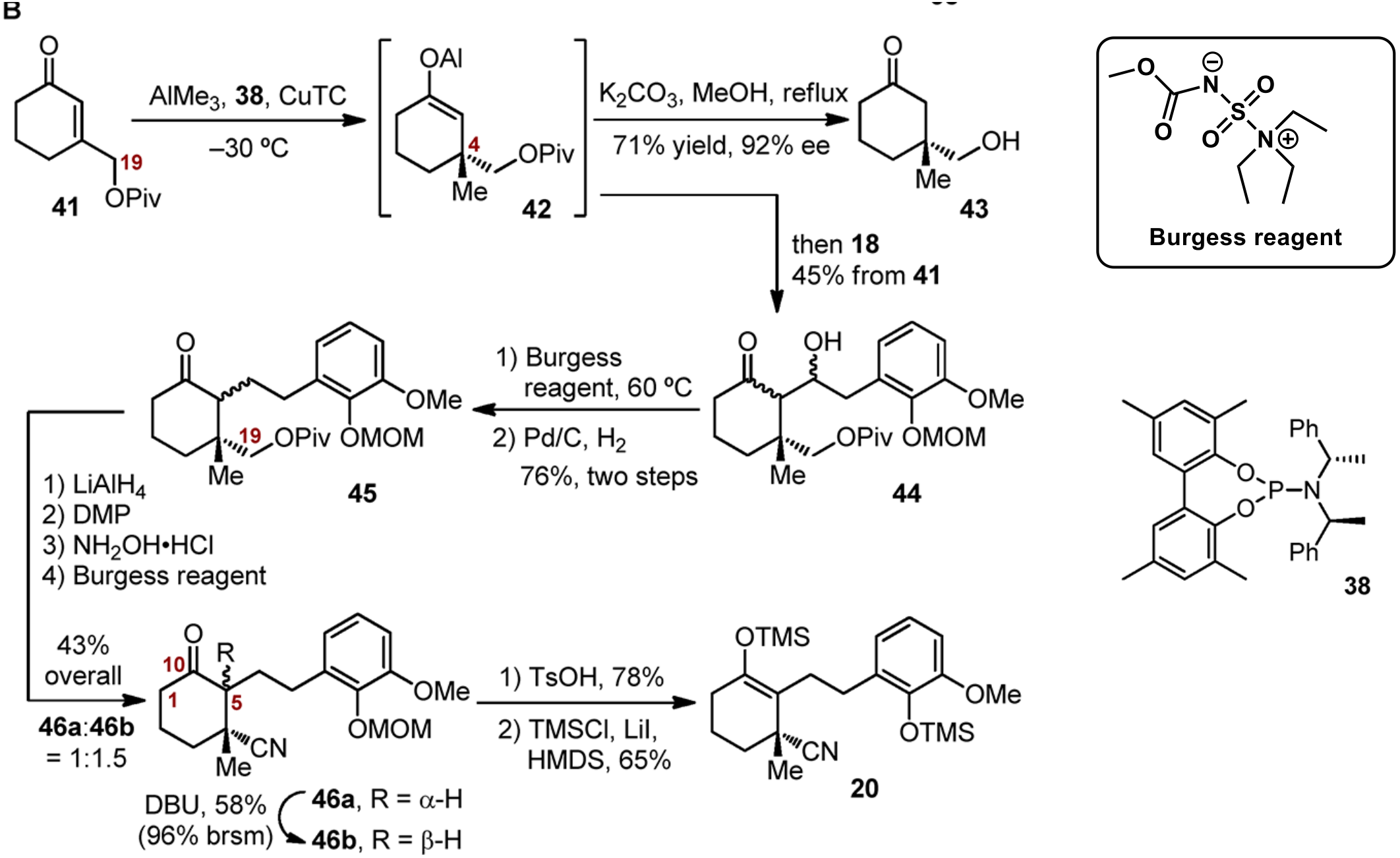
Scheme 6. Completion of the Total Synthesis of(±)-Arcutinine (2)



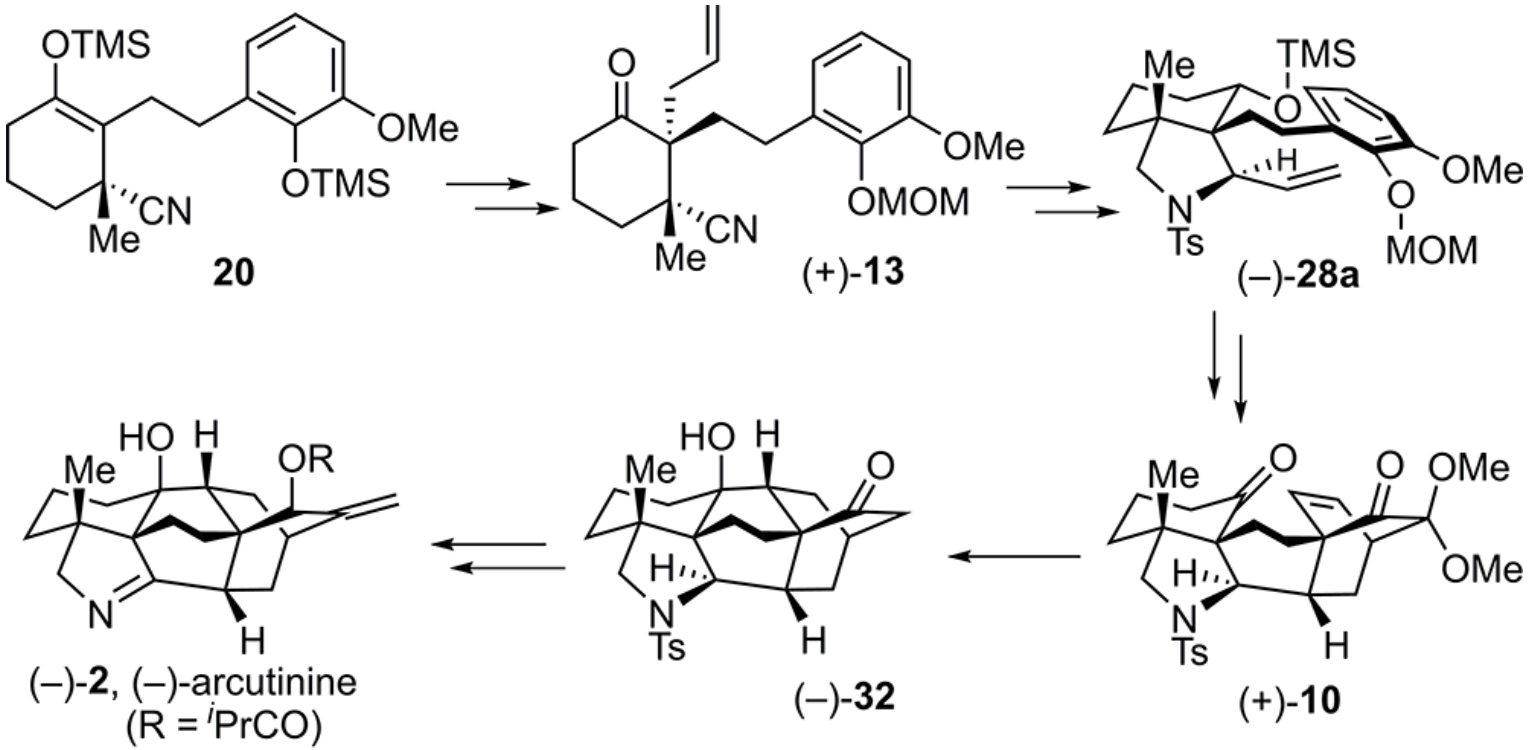
Scheme 7. Unsuccessful Asymmetric Conjugate Additions and Preparation of the Enantioenriched Intermediate 20

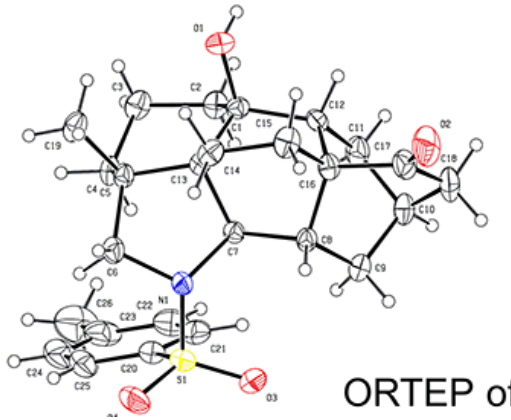


B

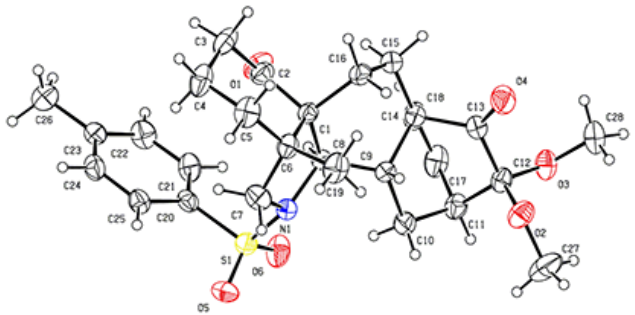

AlMe3, 38, CuTC
–30 °C
K2CO3, MeOH, reflux
71% yield, 92% ee
then 18
45% from 41
1) Burgess reagent, 60 °C
2) Pd/C, H2
76%, two steps
1) LiAlH4
2) DMP
3) NH2OH•HCl
4) Burgess reagent
43% overall
46a:46b = 1:1.5
DBU, 58% (96% brsm)
46a, R = α-H
46b, R = β-H
1) TsOH, 78%
2) TMSCl, LiI, HMDS, 65%
41
42
43
44
45
20
Burgess reagent
38

Scheme 8. Enantioselective Total Synthesis of (−)-Arcutinine





ORTEP of (–)-**32**



ORTEP of (+)-**10**