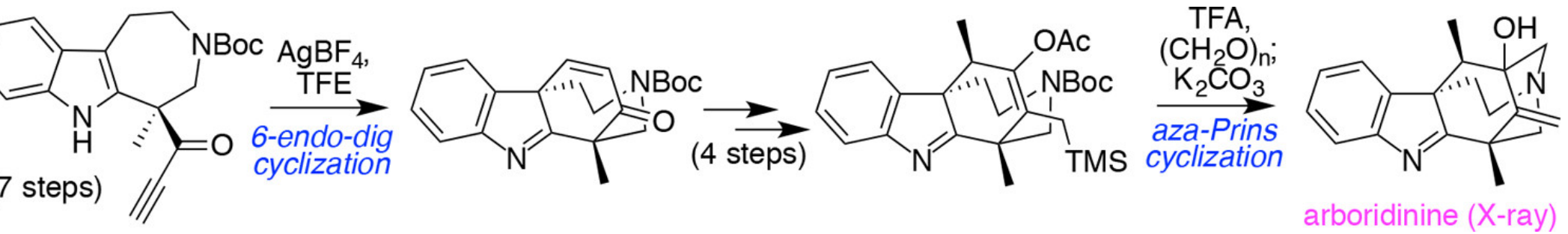


Total Synthesis of the Caged Indole Alkaloid Arboridinine Enabled by aza-Prins and Metal-Mediated Cyclizations

Bart Herleì, Martin J. Wanner, Jan H. van Maarseveen, and Henk Hiemstra DOI: 10.102 jacs.7b07724

LIMING CAO

WIPF GROUP CURRENT LITERATURE

1/27/2018

Indole Alkaloid Arboridinine from *Kopsia arborea* Blume

oridinine was isolated from *Kopsia arborea* Blume found in Malaysia by Kam and orkers in 2015 (1.5 mg/kg plant material).

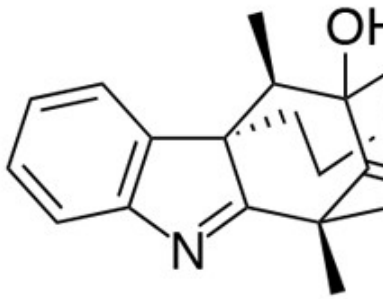
plant is widely distributed in Southeast Asia, India, China, and Australia. It is a ll tree up to 15-20 ft high with leathery leaves and white fragrant flowers owed by showy prune colored fruit.

used to treat edema with the extract of its bark and tonsillitis with its fruit and es.

P., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724
, S. P., et al. *Org. Lett.* **2015**, 17, 3628
://toptropicals.com/catalog/uid/Kopsia_arborea.htm
//kplant.biodiv.tw/雲南蕊木/雲南蕊木.htm

Indole Alkaloid: Arboridinine

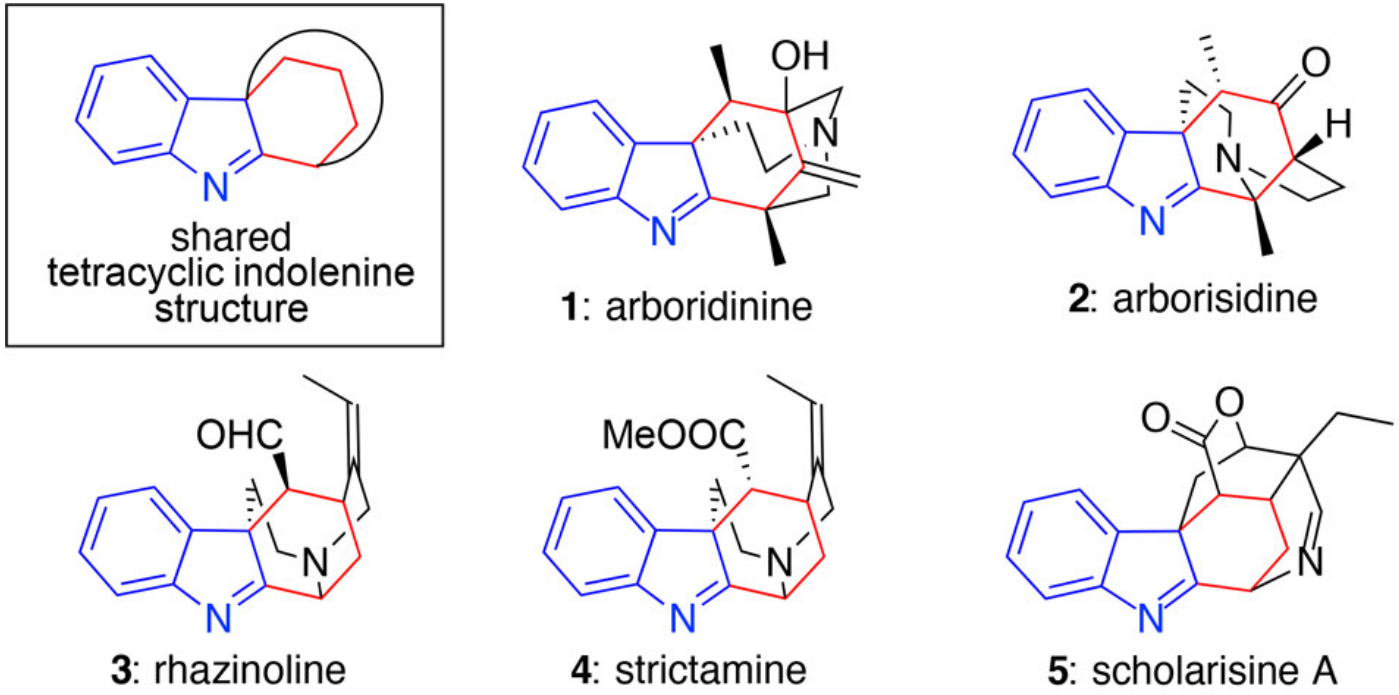
- The natural product possesses an unprecedented cage skeleton that includes multiple rings of varying individual size (6- and 7-membered, as well as an indolenine heterocycle).
- It also includes two all-carbon quaternary centers as well as a tertiary alcohol.
- Arboridinine did not show any appreciable cytotoxicity against both drug-sensitive as well as vincristine-resistant KB cells.
- It showed a moderate concentration dependent relaxation effect on phenylephrine-induced contraction in isolated rat aortic rings (EC_{50} 4.98 μM, E_{max} 60.6 ± 7.8%; cf. isoprenaline, EC_{50} 0.08 μM, E_{max} 79.7 ± 4.2%).



arboridinine

et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724
S. P., et al. *Org. Lett.* **2015**, 17, 3628
H., et al. *J. Nat. Prod.* **2008**, 71, 289
, H., et al. *Bioorg. Med. Chem*. **2011**, 19, 4075

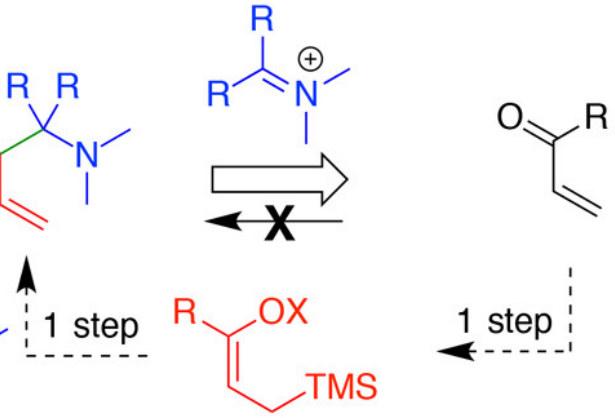
Structure of Arboridinine and Its Shared Patterning with Other Alkaloids



- Arboridinine has a tetracyclic indolenine structure also found in other Kopsia-derived alkaloids

., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

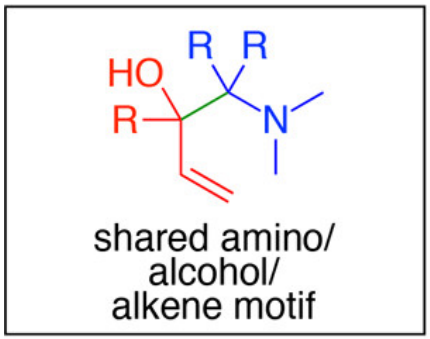
Structure of Arboridinine and Its Shared Patterning with Other Alkaloids

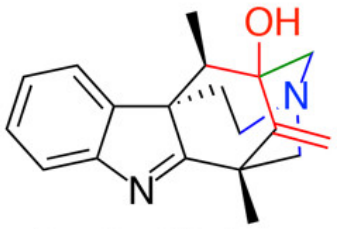


Potential aza-Prins precursor?

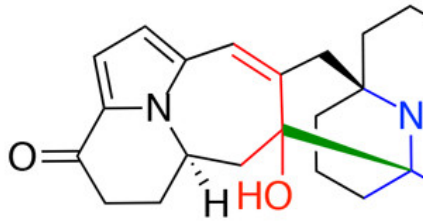
ger in an ionic manner would be
n umpolung type-difficult.

ygenated allylic silane with X
enting the enol carbon from
ng as a nucleophile.

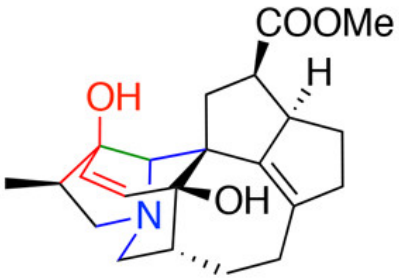




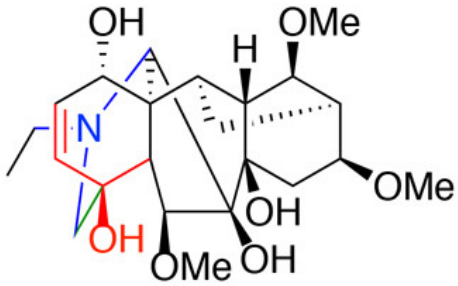
1: arboridinine



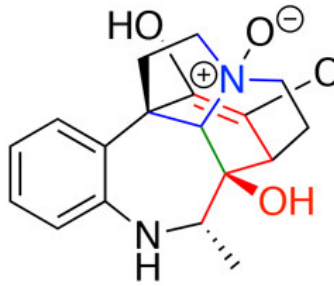
6: chilocorine D



7: daphmacromine K



8: puberunine D

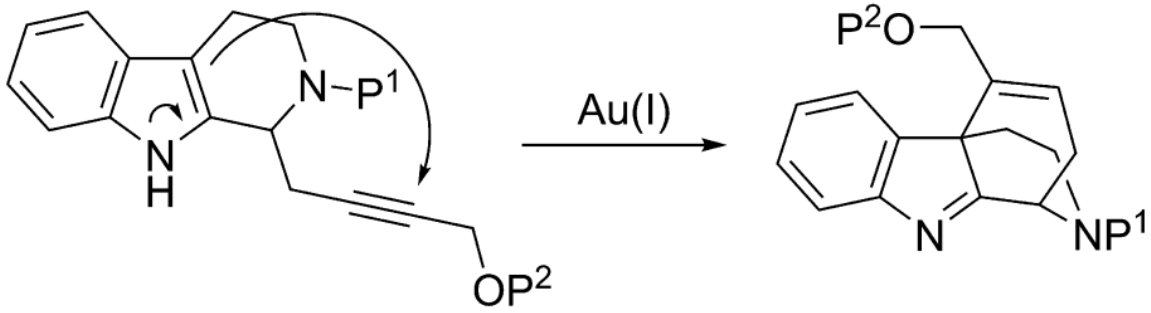


9: kopsiyunnanin

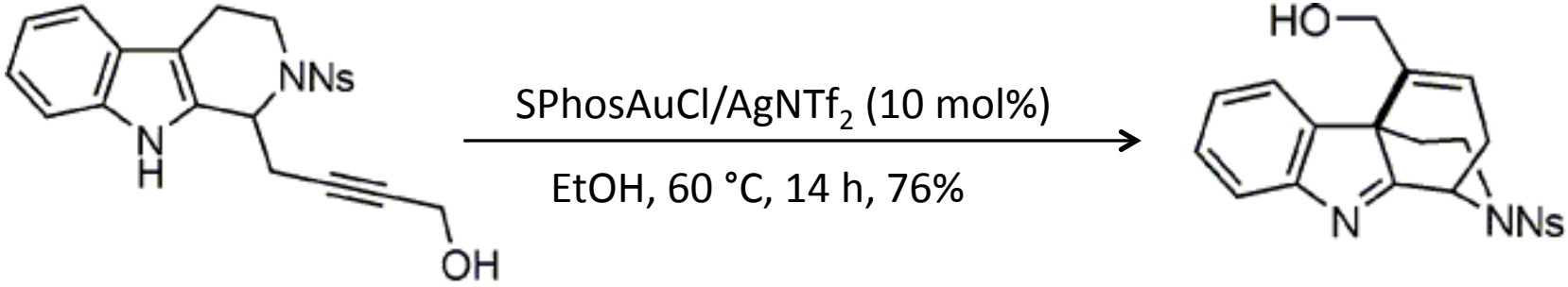
- Shared patterning of the alkene, tertiary alcohol a neighboring amine a potential construction via an *aza*-Prins reaction.

. et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

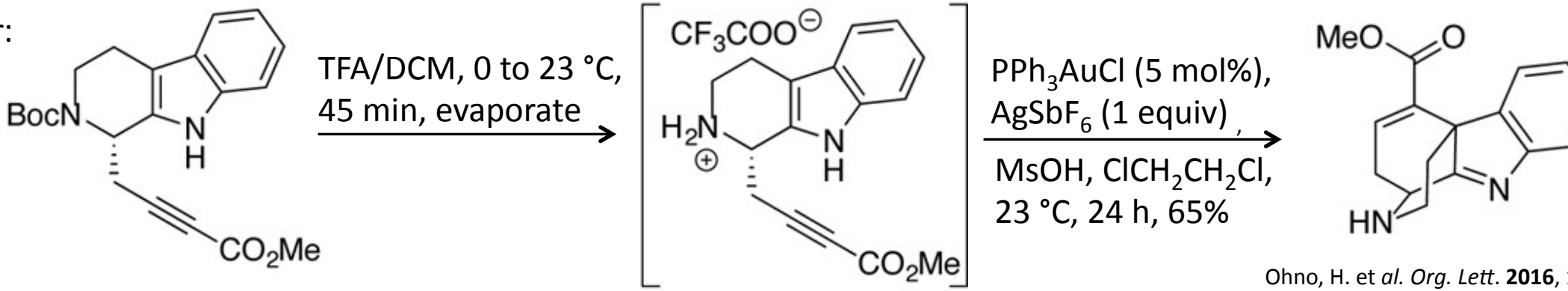
Gold-catalyzed 6-*endo*-dig Cyclization



Ohno:

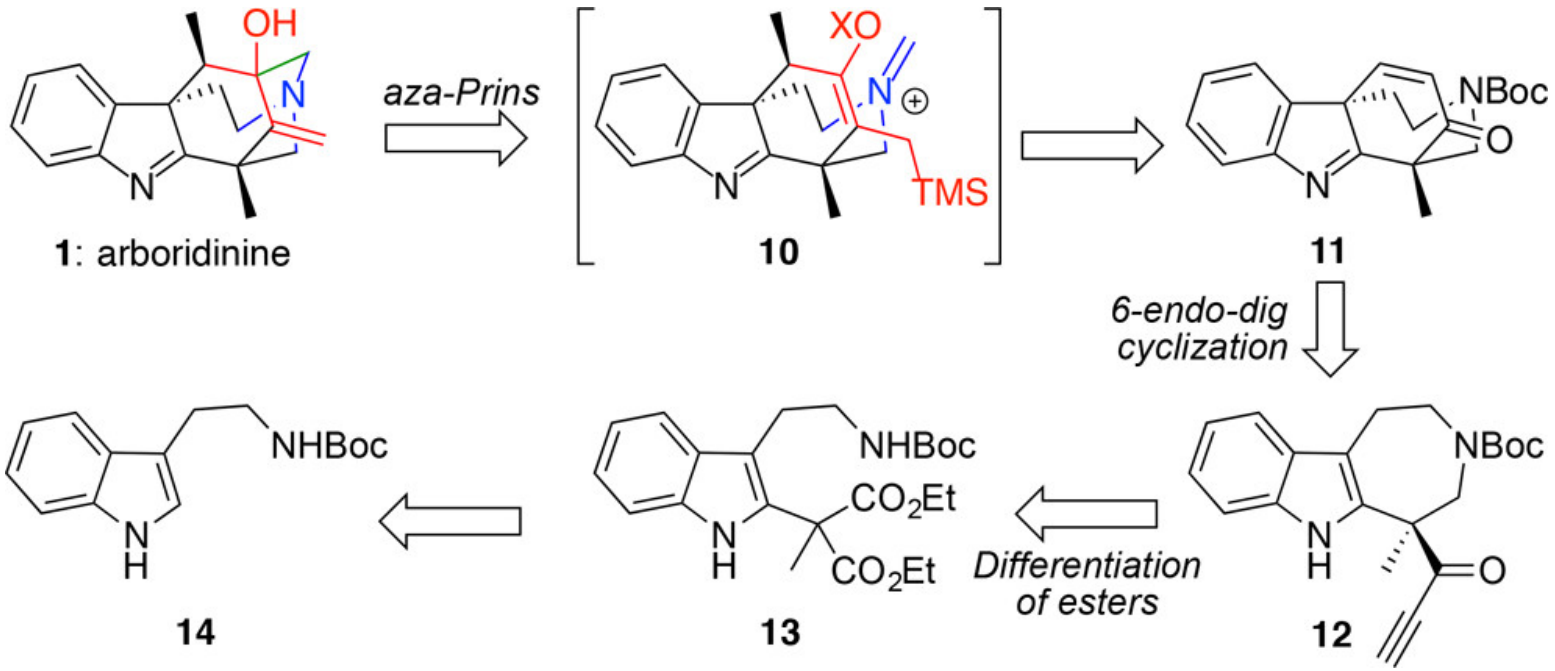


r:



Ohno, H. et *al. Org. Lett*. **2016**, 1
Smith, M. W. et al. *Org. Lett*. **201**

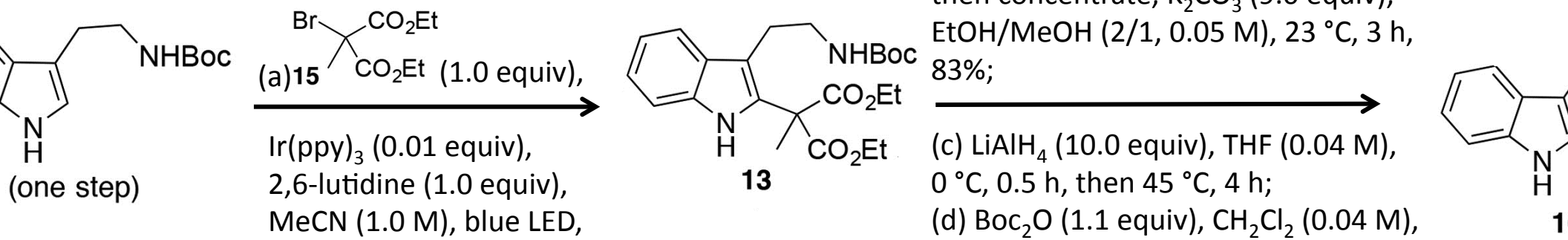
Retrosynthetic Analysis of Arboridinine Based on Two Key Cyclizations



- The particular cyclization strategy requires the synthesis of one of the 7-membered rings early in the sequence.
- The synthesis of 7-membered ring in an asymmetric manner requires the differentiation of the two esters within a precursor such as **13**.

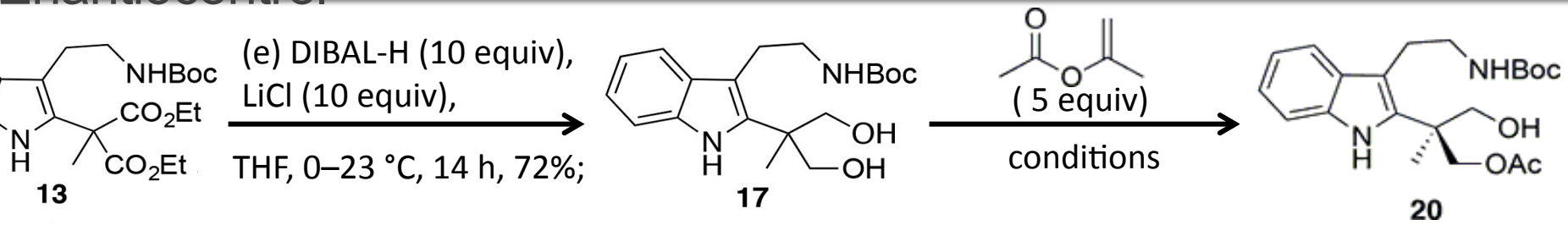
., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

Syntheses of Aldehyde **16** in Racemic Formats



., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

Screening of Conditions To Achieve the Mono-acetylation of Diol **17** with Enantiocontrol

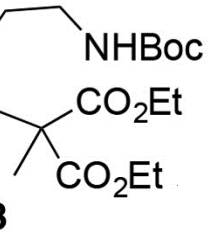


y	conditions	conversion (%)[a,b]	ee (%)[c]
	Candida cylindrica lipase, EtOAc, 40 °C, 48 h	NR	
	Pseudomonas cepacia lipase, EtOAc, 40 °C, 48 h	NR	
	Pseudomonas fluorescens lipase, EtOAc, 40 °C, 48 h	NR	
	pig liver esterase, EtOAc, 40 °C, 48 h	NR	
	porcine pancreatin, EtOAc, 40 °C, 48 h	NR	
	Candida antarctica lipase, EtOAc, 23 °C, 24 h	NR	
	Candida antarctica lipase, EtOAc, 40 °C, 216 h	39	34
	Candida antarctica lipase, EtOAc, 40 °C, 48 h	10–20	60
	Candida antarctica lipase, EtOAc, 80 °C, 24 h	50	20
	Candida antarctica lipase, THF, 40–60 °C, 48 h	<10	ND
	Candida antarctica lipase, CH_2Cl_2, 40–60 °C, 48 h	<10	ND
	Candida antarctica lipase, pH 7.4 phosphate buffer, 40–60 °C, 48 h	NR	

- a For all but entry 7, the given reflects conversion product based on NMR analysis; in the case of e an isolated yield was obt
- b NR = no reaction.
- c ND = not determined.

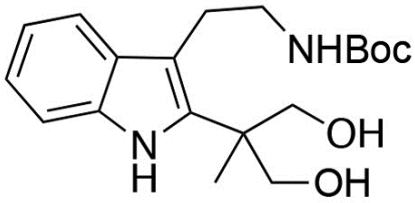
., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

Syntheses of Aldehyde **16** in Enantioenrichd Formats



(e) DIBAL-H (10 equiv),
LiCl (10 equiv),

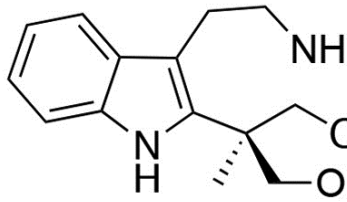
THF, 0–23 °C, 14 h, 72%;



17

(f) $CuCl_2$ (0.1 equiv), **18** (0.1 equiv),
BzCl (1.5 equiv), Et_3N (1.1 equiv),

CH_2Cl_2 (0.1 M), −78 °C, 14 h, 72%;

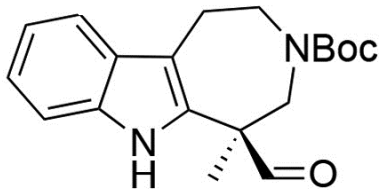


19

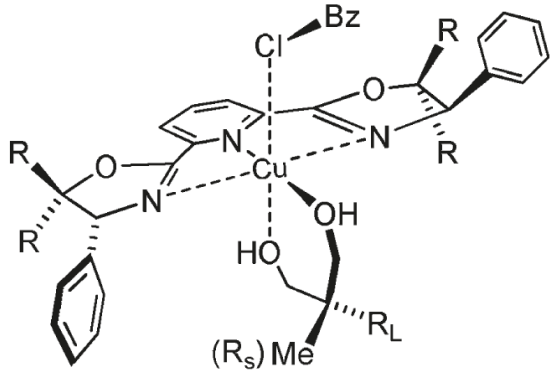
5 equiv), DMSO (0.15 M),

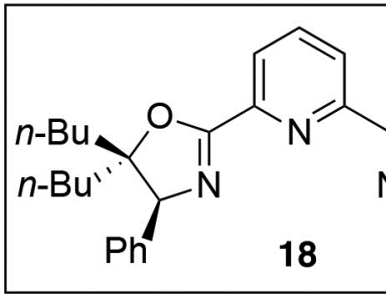
(2.5 equiv), TFA (0.85 equiv),
1 M), 0–23 °C, 18 h, 68%
steps, 96% *ee*;

5.0 equiv), MeOH (0.1 M),
1 M), 23 °C, 0.75 h;
equiv), DMSO (0.1 M), 23
1% over two steps.



16



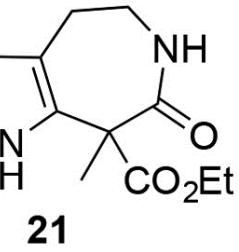


18

., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724
Y., et al. *J. Am. Chem. Soc.* **2011**, 133, 1772.

Explorations into a Potential Tsuji–Trost Allylation Strategy To Achieve an Alternate

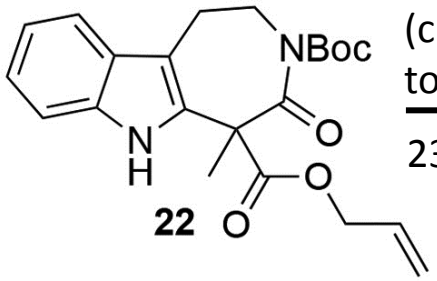
Synthesis of Aldehyde **16**



21

(a) allyl alcohol/THF (5/2, 0.1 M), NaH (1.5 equiv), 23 °C, 3 h, 93%;

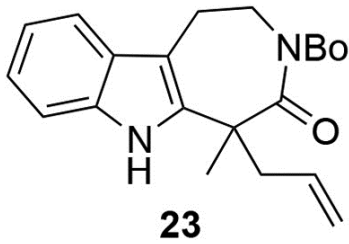
(b) Boc_2O (1.3 equiv), 4-DMAP (0.1 equiv), Et_3N (3.0 equiv), CH_2Cl_2 (0.065 M), 23 °C, 4 h, 85%;



22

(c) $Pd(PPh_3)_4$ (0.1 equiv), toluene (0.022 M),

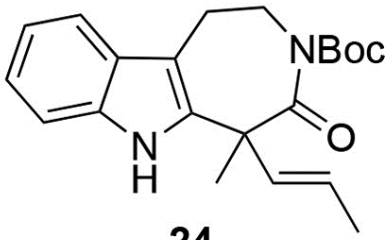
23 °C, 30 min, 98%;



23

$(MeCN)_2$ (0.15 equiv),
e (0.022 M),

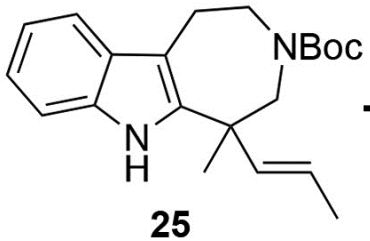
3 h, 57%;



24

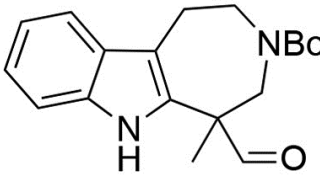
(e) $LiEt_3BH$ (1.5 equiv), THF (0.034 M), −78 °C, 1 h;

(f) TFA (2.0 equiv), Et_3SiH (10 equiv), CH_2Cl_2 (0.017 M), 0 °C, 15 min, 64% over two steps.



25

X

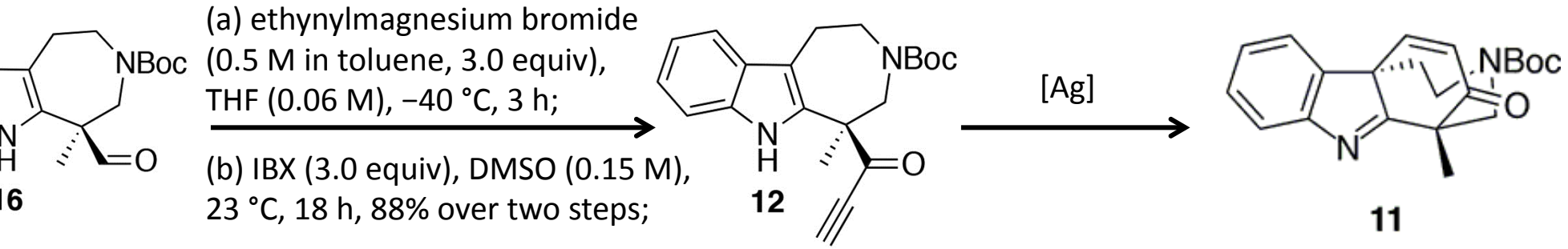


16

$OsO_4/NaIO_4$ conditions and standard ozonolysis; Unsuccessful oxidative cleavage with **24**

., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

Screening of Conditions for the Ag-Based 6-endo-Dig Cyclization of **12** T Generate Polycycle **11**

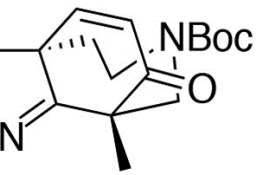


try	conditions[a]	yield (%)
	$AgBF_4$ (1 equiv), CH_2Cl_2, 0 °C, 20 min	63
	$AgBF_4$ (0.1 equiv), THF, 25 °C, 15 h	57
	$AgBF_4$ (0.1 equiv), EtOH, 25 °C, 15 h	41
	$AgBF_4$ (0.1 equiv), iPrOH, 25 °C, 15 h	74
	$AgBF_4$ (0.1 equiv), TFE, 0 °C, 2 h	75
	$AgBF_4$ (0.1 equiv), HFIP, 0 °C, 1 h	40
	AgOTf (0.1 equiv), TFE, 0 °C, 1 h	66
	$AgNTf_2$ (0.1 equiv), TFE, 0 °C, 1 h	59
	AgOAc (0.1 equiv), TFE, 0 °C, 1 h	56

- a The reaction temperature and time reflect the temperature and time needed for full consumption of the starting material. HFIP = hexafluoroisopropanol.

., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

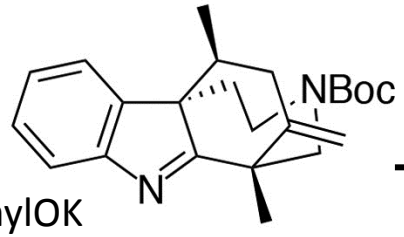
Completion of Total Synthesis of Arboridinine 1



11

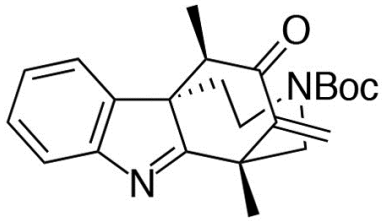
(d) CuI (3.0 equiv), MeLi
(1.6 M in Et_2O, 6.0 equiv),
THF (0.03 M), −78 to 0 °C,
4 h, 98%;

(e) Ph_3PCH_3Br (5.0 equiv), *t*AmylOK
(1.4 M in toluene, 4.0 equiv),
toluene (0.06 M), 80 °C, 1 h, 95%;



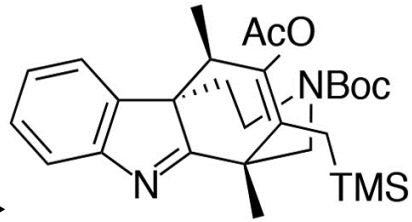
26

(f) SeO_2 (10.0 equiv),
1,4-dioxane, 80 °C, 8 h,
50%;



27

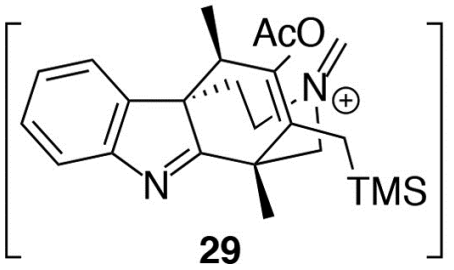
amethyldisilane (10 equiv),
.6 M in Et_2O, 9.0 equiv),
1.0 M), 0 °C, then **27** (1.0 equiv),
0 equiv), THF (0.1 M) −78 °C, 30 min;



28

(h) TFA/CH_2Cl_2 (1/2, 0.01 M),
23 °C, 0.5 h remove volatiles,
redissolve in CH_2Cl_2,

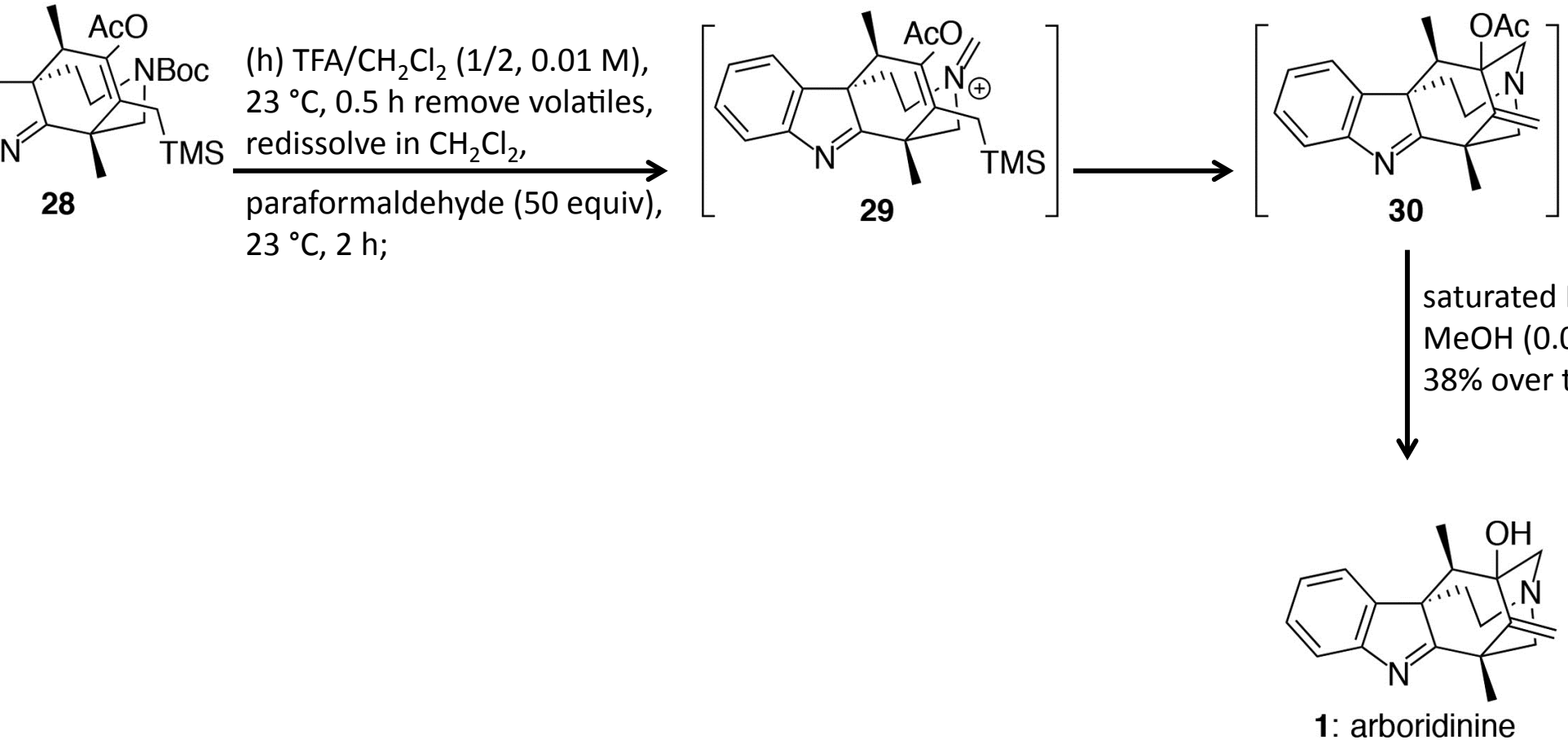
paraformaldehyde (50 equiv),
23 °C, 2 h;



29

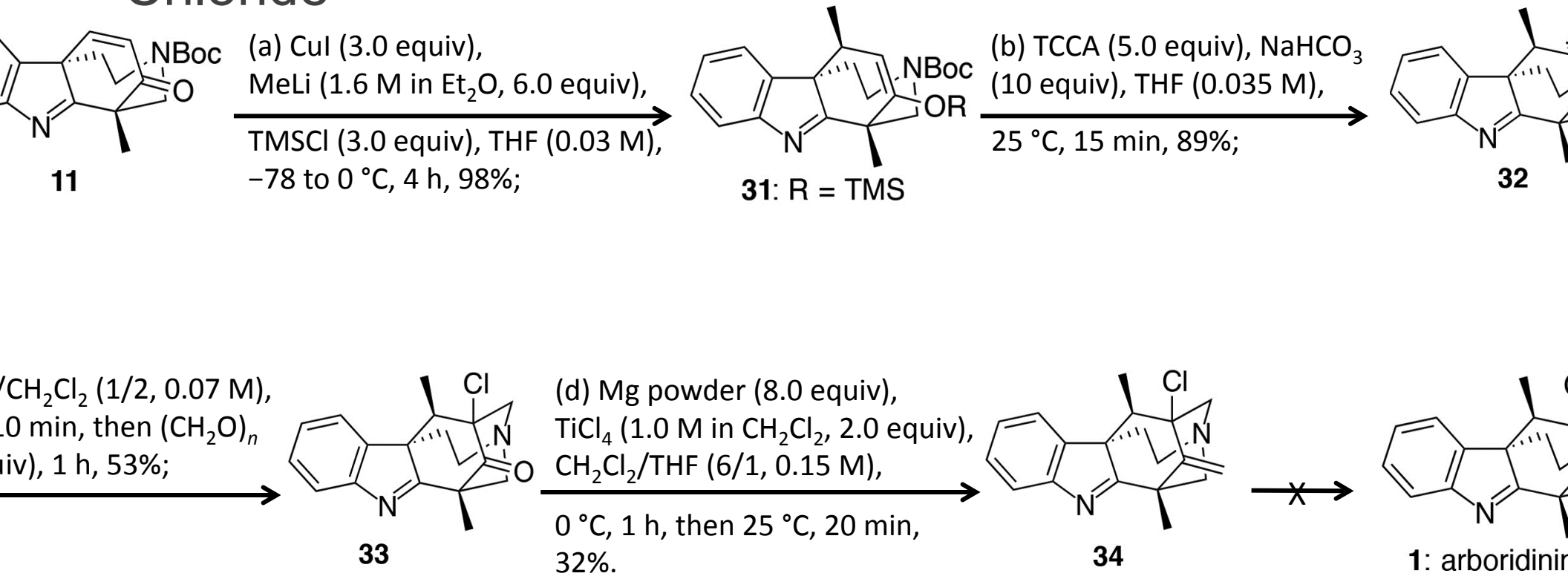
., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

Completion of Total Synthesis of Arboridinine **1**



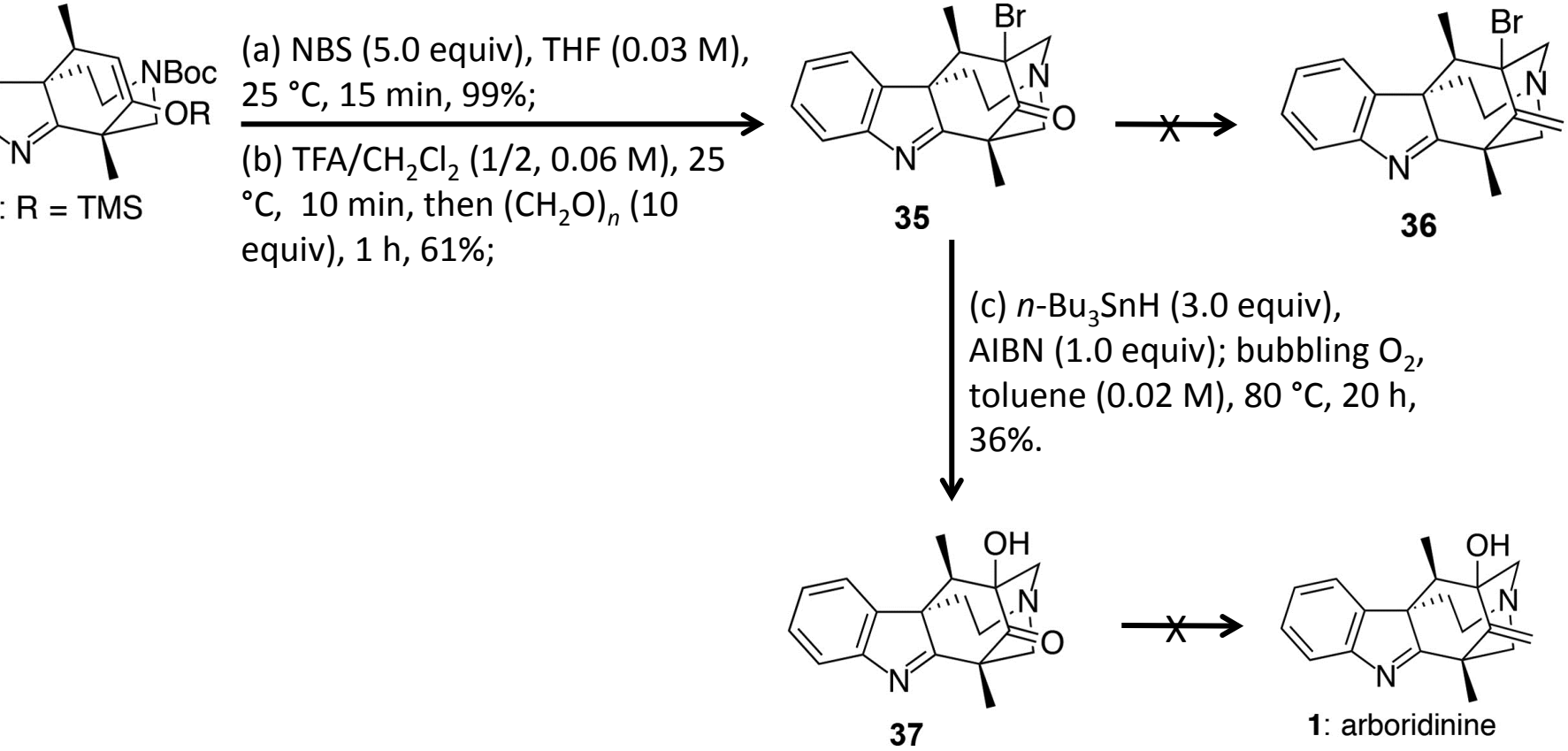
., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

Other Iminium-Based Cyclization Strategies-Tertiary Chloride



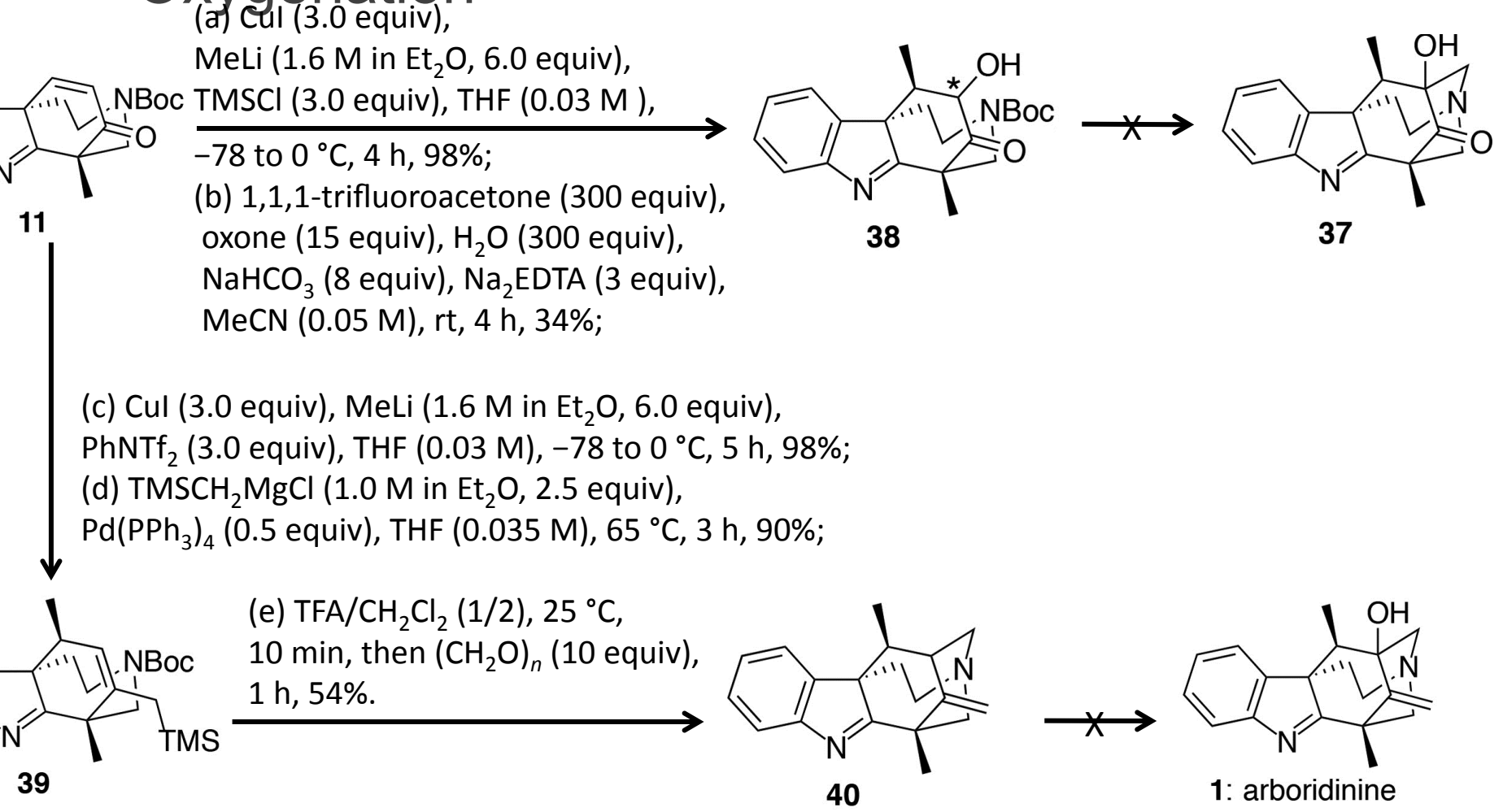
J. Am. Chem. Soc. DOI: 10.1021/jacs.7b07724

Other Iminium-Based Cyclization Strategies-Tertiary Bromide



., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

Other Iminium-Based Cyclization Strategies-Direct Oxygenation



., et al. *J. Am. Chem. Soc*. DOI: 10.1021/jacs.7b07724

Conclusion

concise synthesis of the unique alkaloid arboridinine was developed with a number of emoselective reactions and critical cyclization chemistries inspired by searching for elements of uctural homology with other alkaloid targets.

e terminating aza-Prins cyclization proved critical to establishing the full array of functionality the target, and new scope in terms of metal-mediated 6-*endo*-dig cyclizations was also covered.