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Article

Total Synthesis of (−)-Mitrephorone A Enabled by Stereoselective Nitrile Oxide Cycloaddition and Tetrasubstituted Olefin Synthesis

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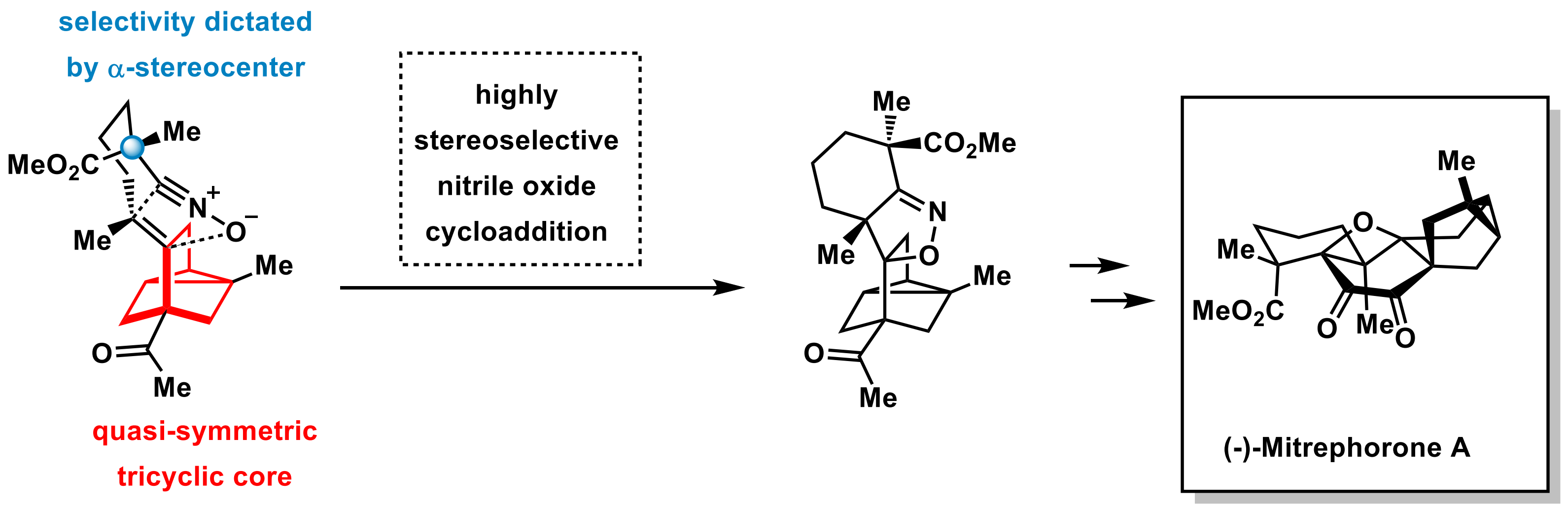
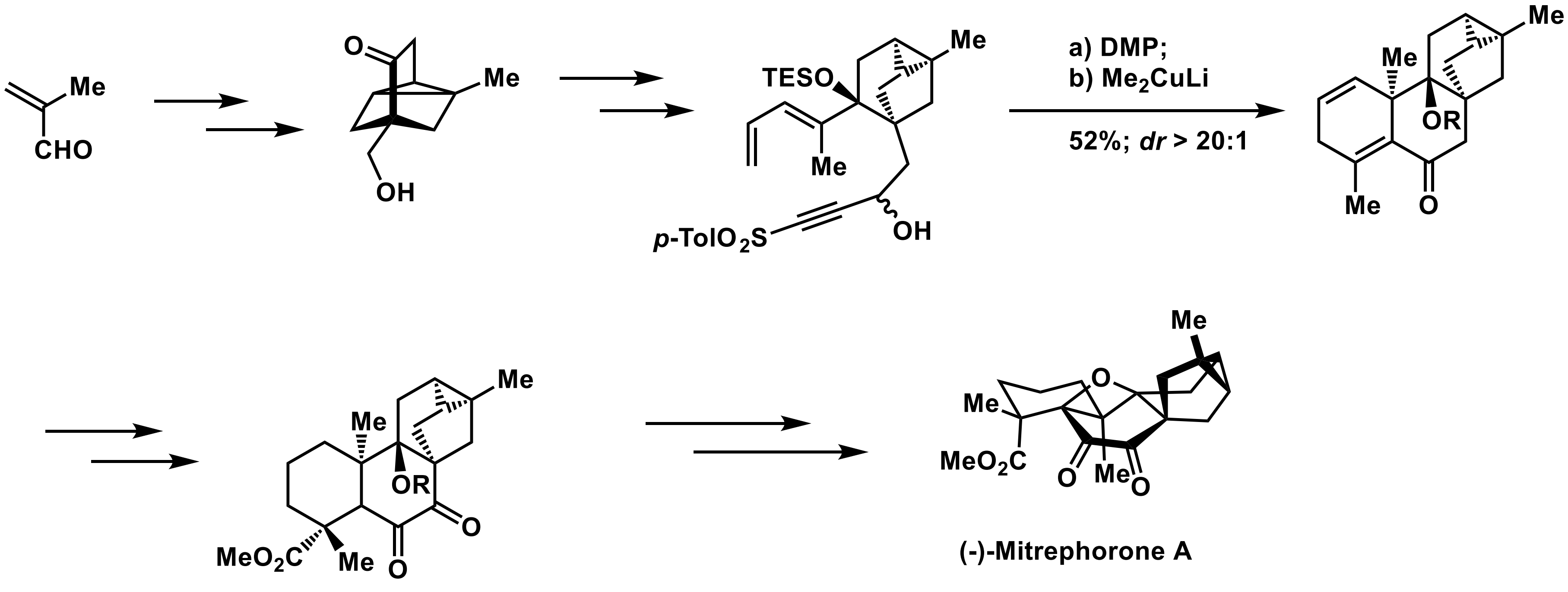


- Tricyclo [3.2.1.0^{2,7}]octane
- Embedded oxetane
- 1,2-diketone
- Highly congested hexacycle
- 4 quaternary carbons
- 5 contiguous stereocenters

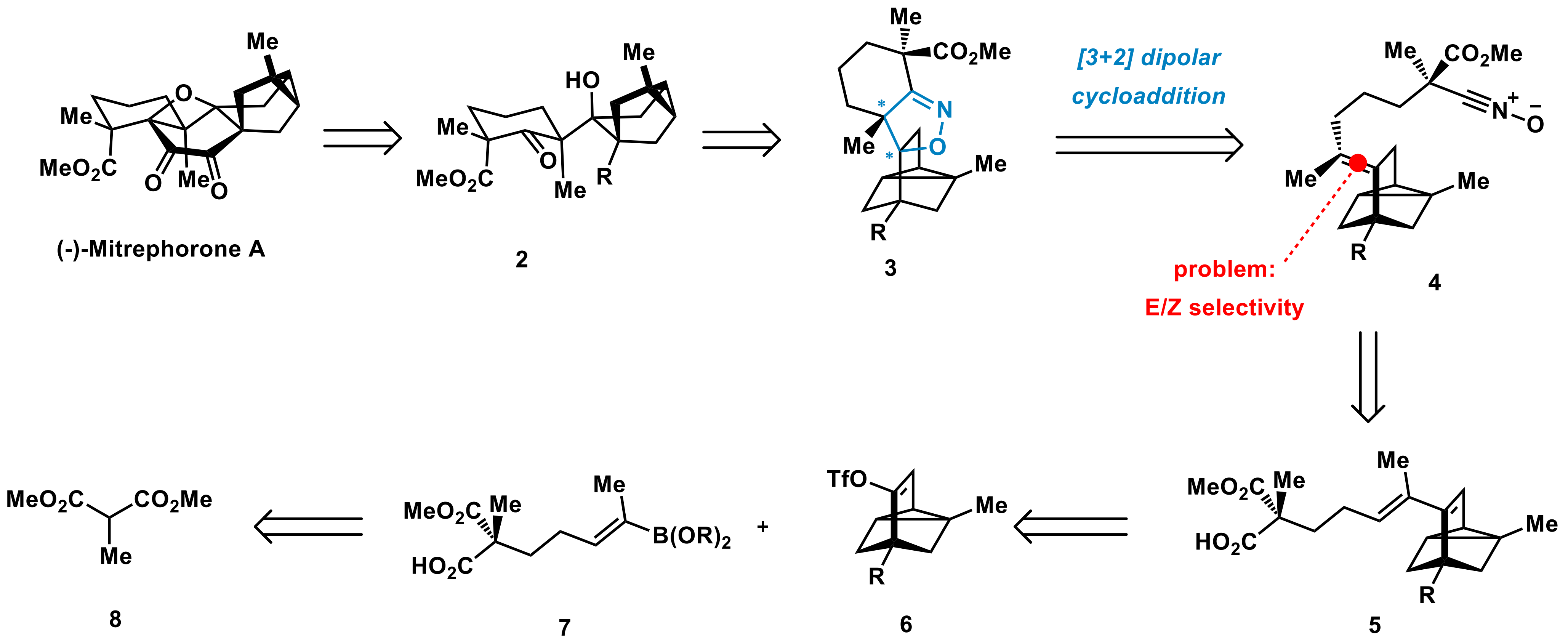
DOI: 10.1021/jacs.0c09520.

Synthesis of (-)-Mitrephorone (A) via [4 + 2] Cycloaddition

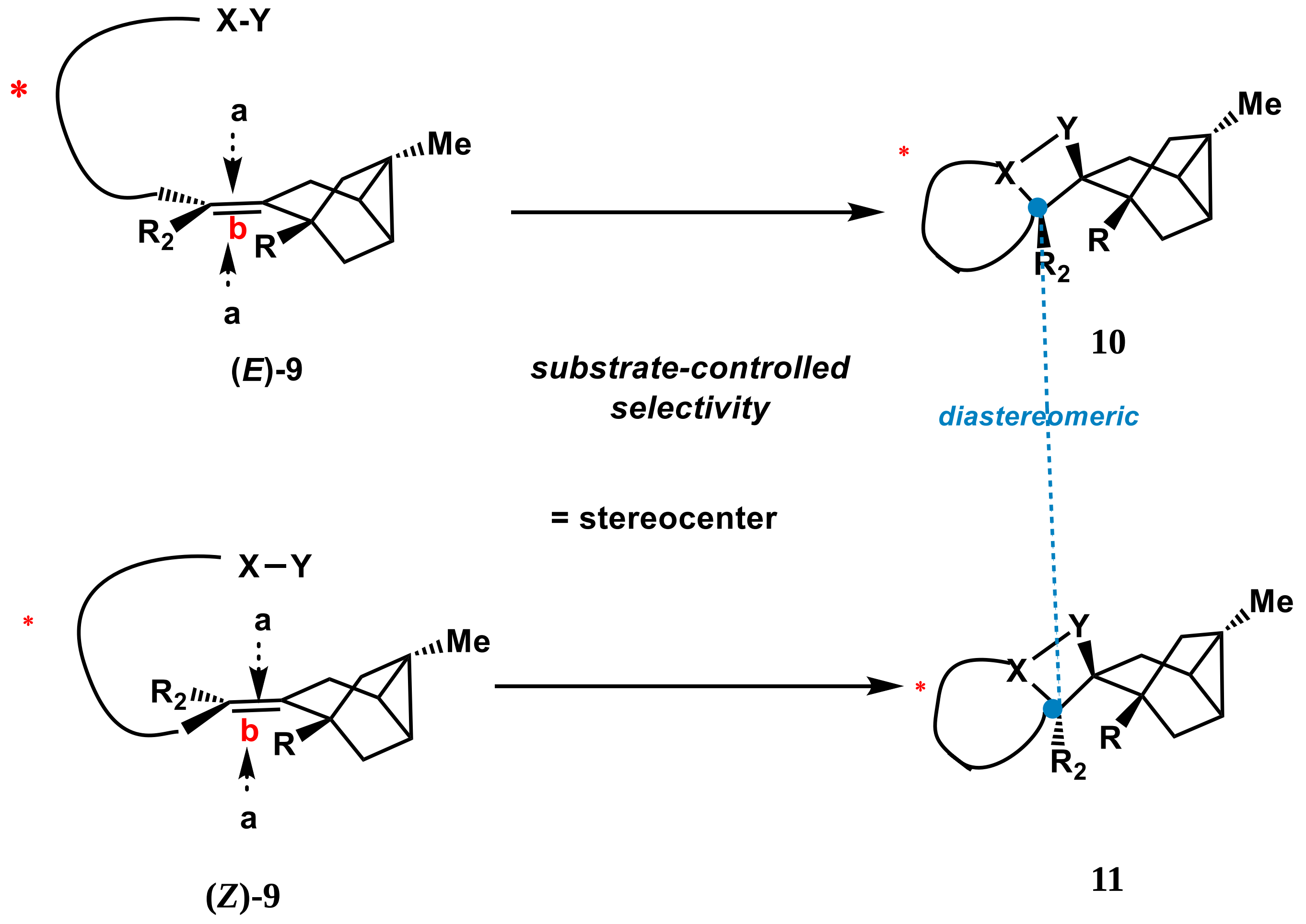


J. Am. Chem. Soc. **2018**, *140*, 16704-16710.

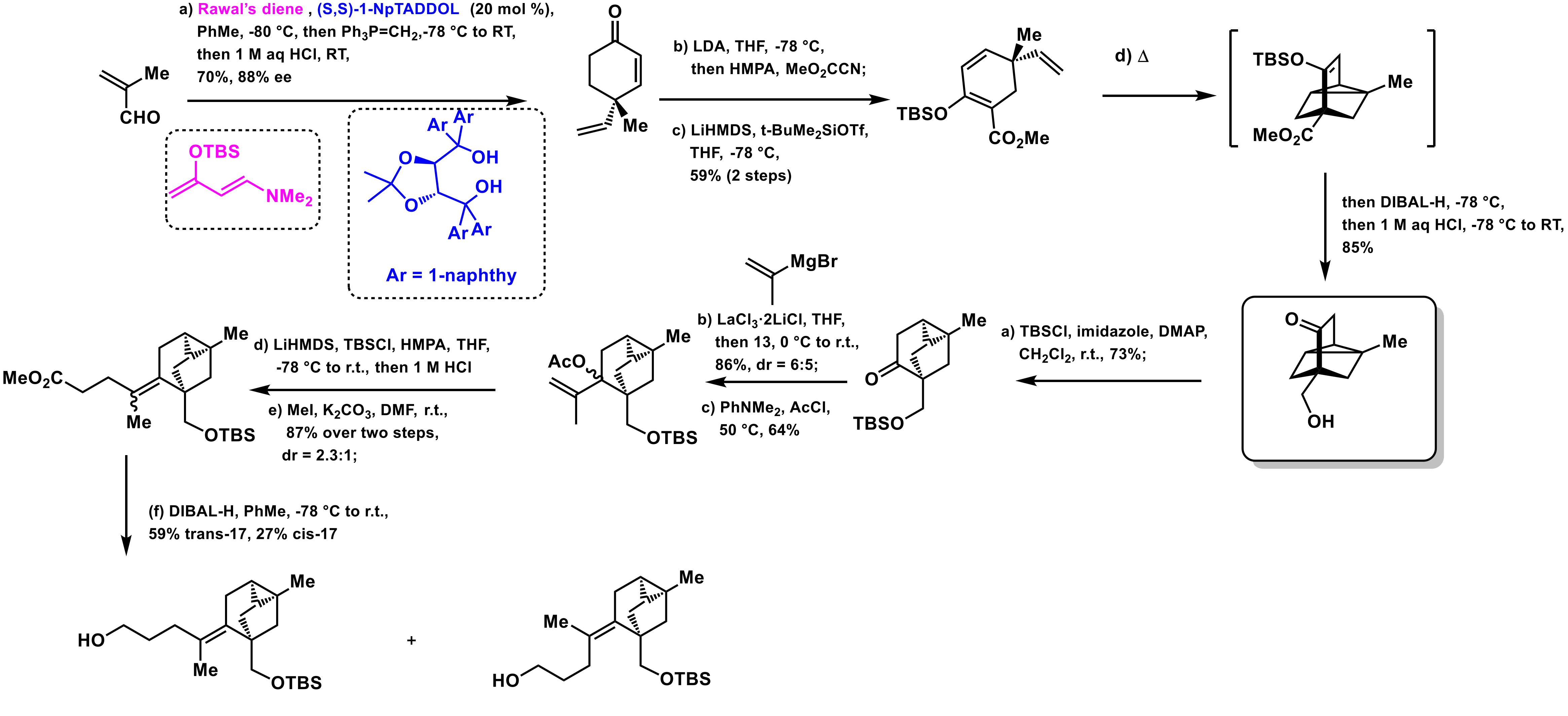
Scheme 1. (−)-Mitrephorone A (1) and Retrosynthetic Analysis



Scheme 2. Stereochemical Considerations Associated with Olefin Functionalization

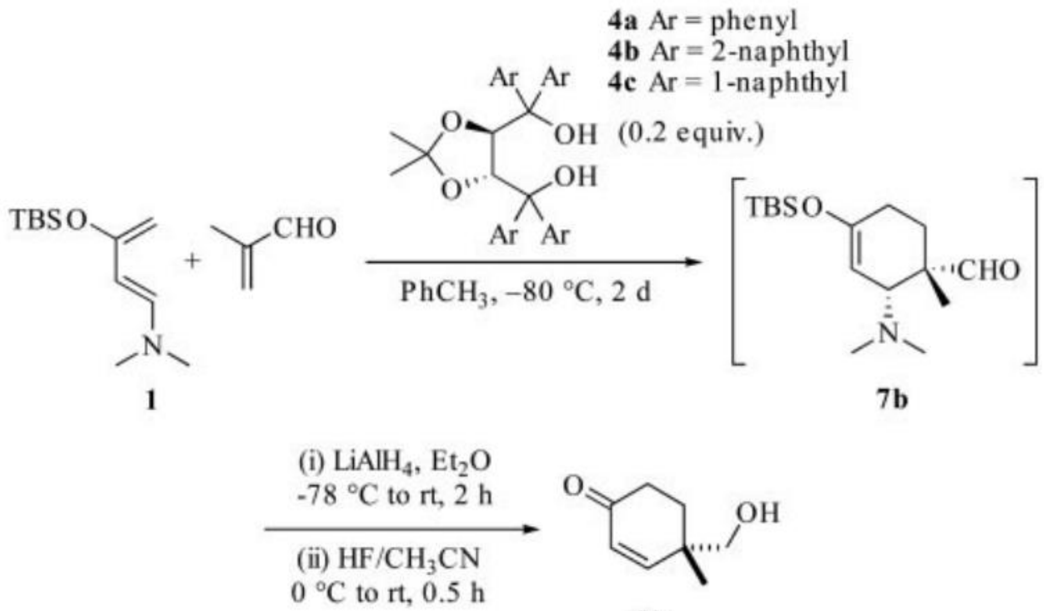


Scheme 3. Synthesis of Tetrasubstituted Olefin via Ireland−Claisen Rearrangement

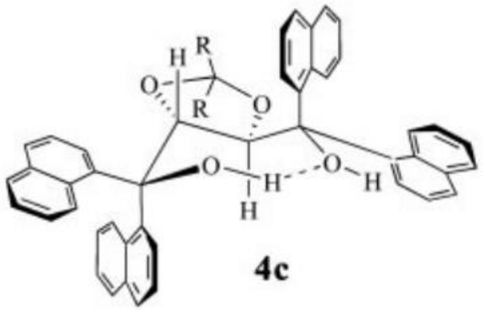


trans - 17 (59%)

cis - 17 (27%)

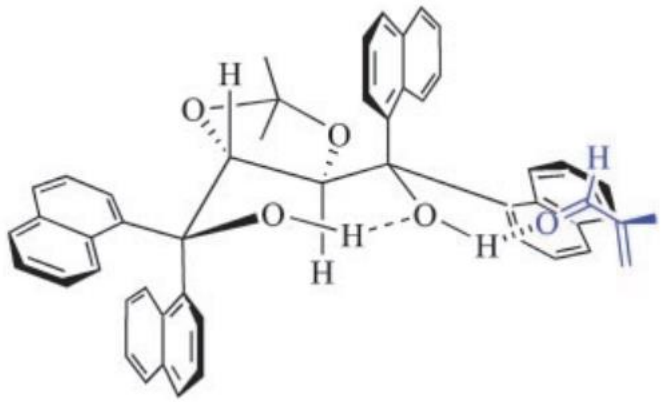


Entry	TADDOL	Yield, %	ee, %
1	**4a**	30	31
2	**4b**	45	33
3	**4c**	83	91



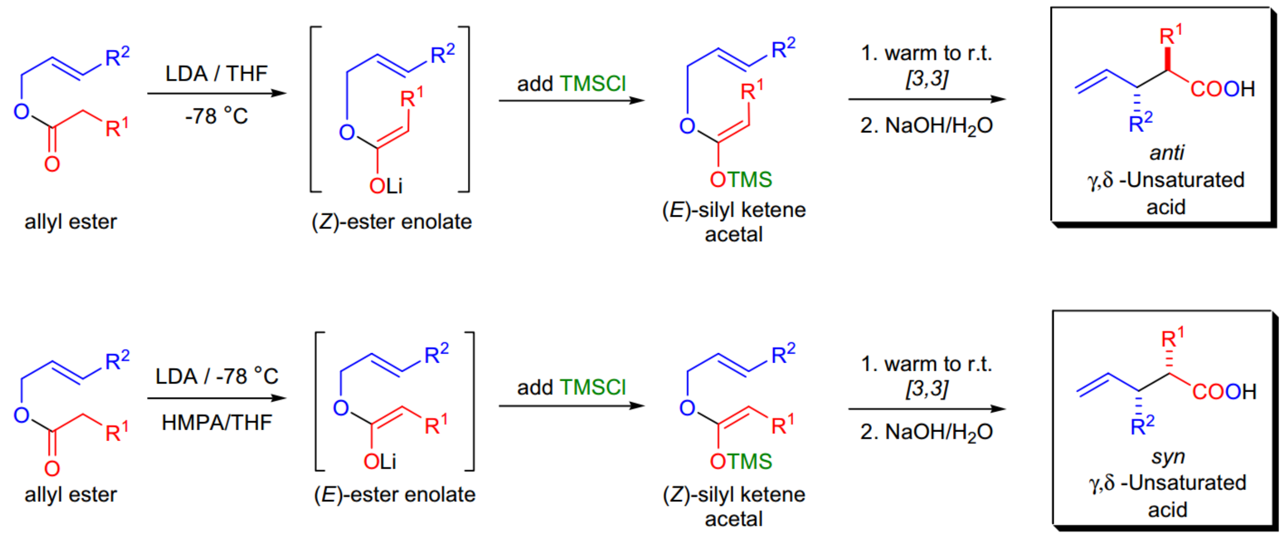
4c

Fig. 1. Solid-state structures of TADDOL **4a–c**.

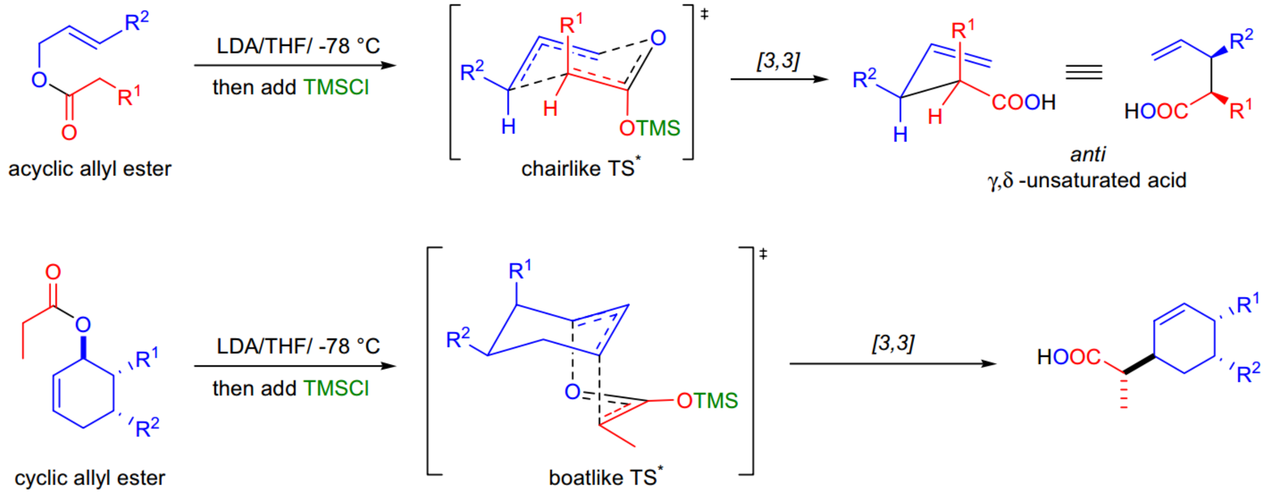


Proc. Natl. Acad. Sci. U. S. A., **2004** *101*, 5846.

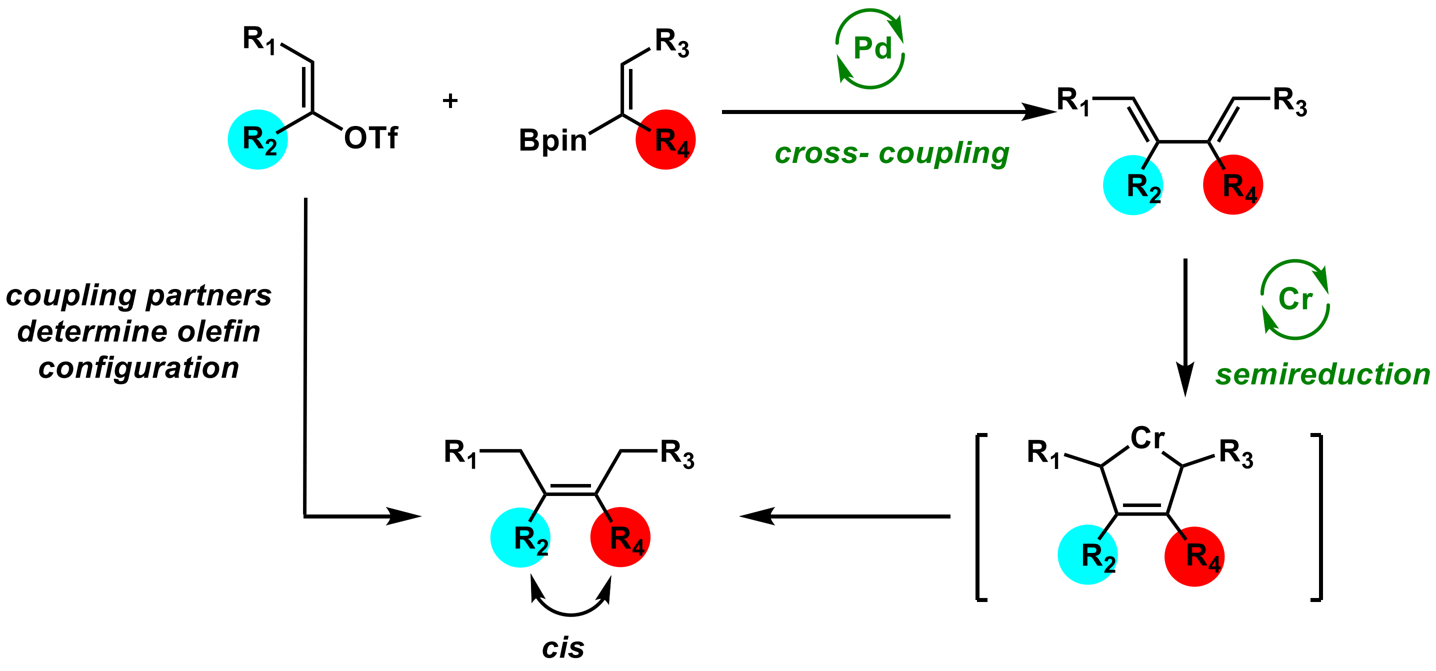
CLAISEN-IRELAND REARRANGEMENT

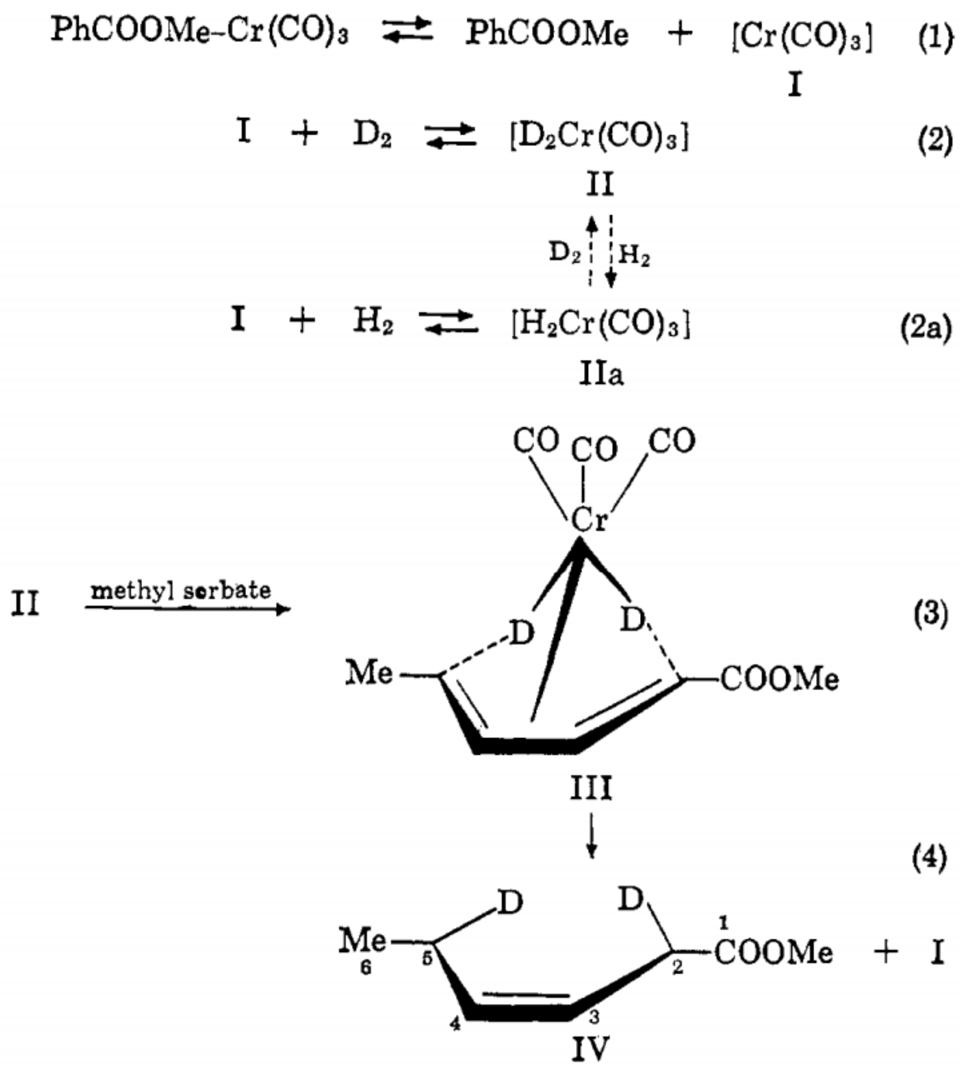


Mechanism:



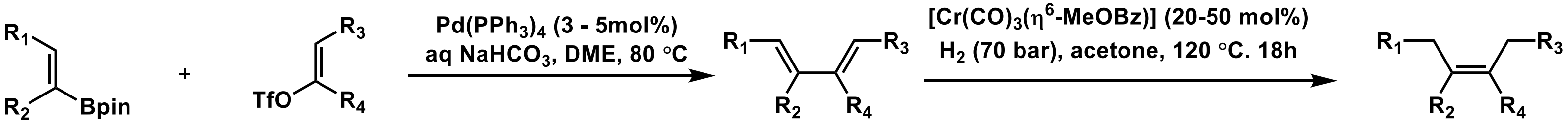
Scheme 4. Conceptual Approach to Tetrasubstituted Olefin Synthesis via Cross-Coupling and 1,4-Semihydrogenation



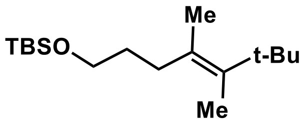


J. Am. Chem. Soc. **1968**, *90*, 2446−2448.

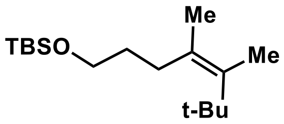
Synthesis of Tetrasubstituted Olefins via Cross-Coupling and Semihydrogenation



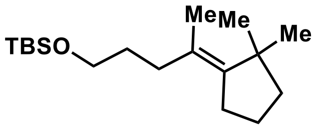
19 20 21



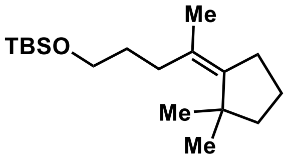
21a
Step 1:98%
Step 2:94%



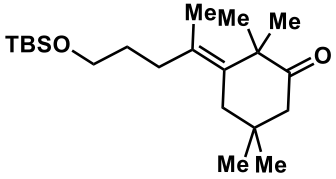
21b
Step 1:67%
Step 2:87%



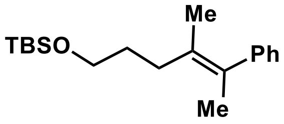
21c
Step 1:99%
Step 2:90%(89%)



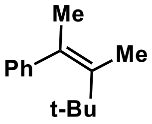
21d
Step 1:75%
Step 2:87%



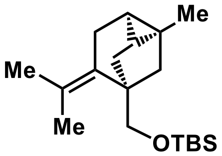
21e
Step 1:97%
Step 2:95%



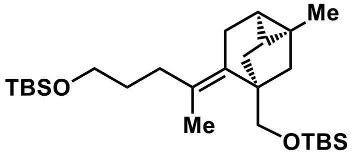
21f
Step 1:97%
Step 2:95%



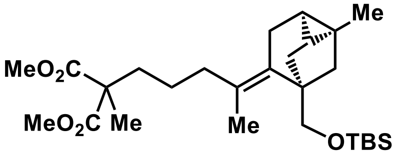
21g
Step 1:79%
Step 2:84%



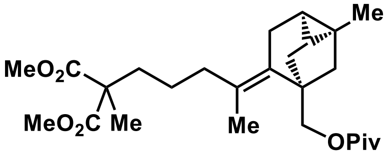
21h
Step 1:65%
Step 2:92%



21i
Step 1:68%
Step 2:90%

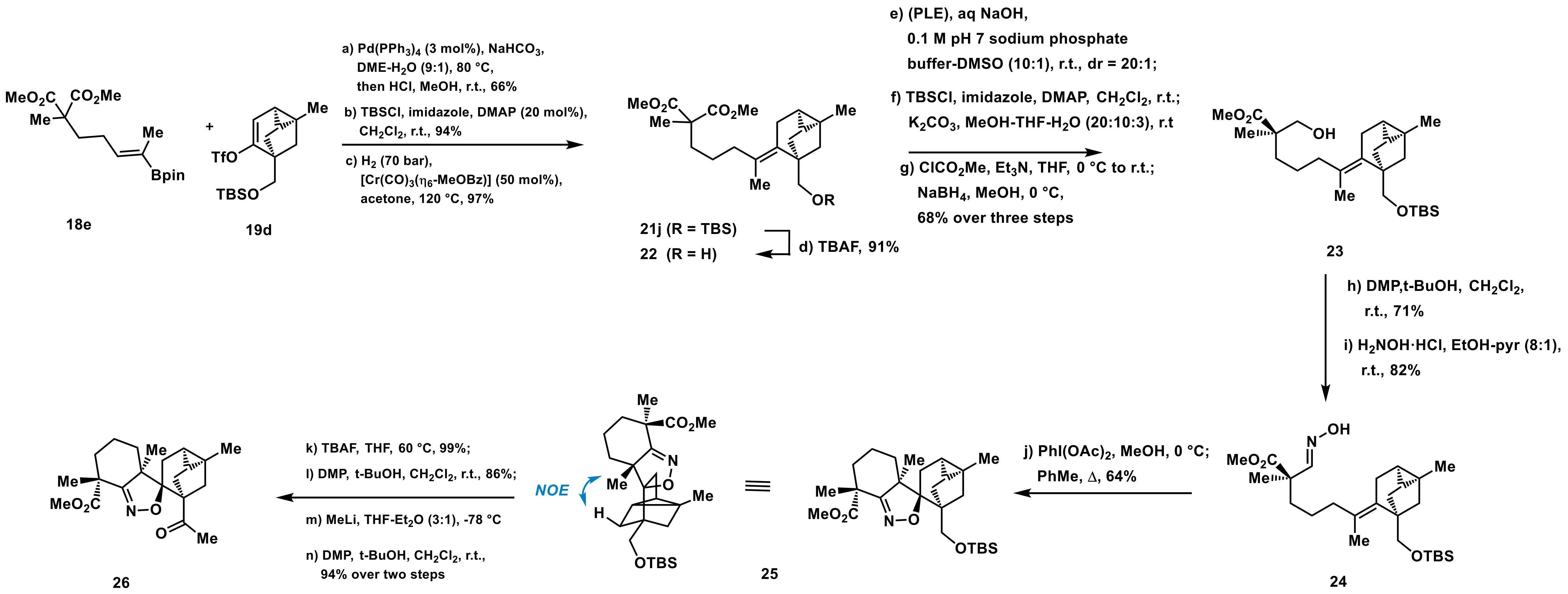


21j
Step 1:62%
Step 2:97%



21k
Step 1:98%
Step 2:98%

Scheme 5. Synthesis of Isoxazoline 26 via Nitrile Oxide Cycloaddition



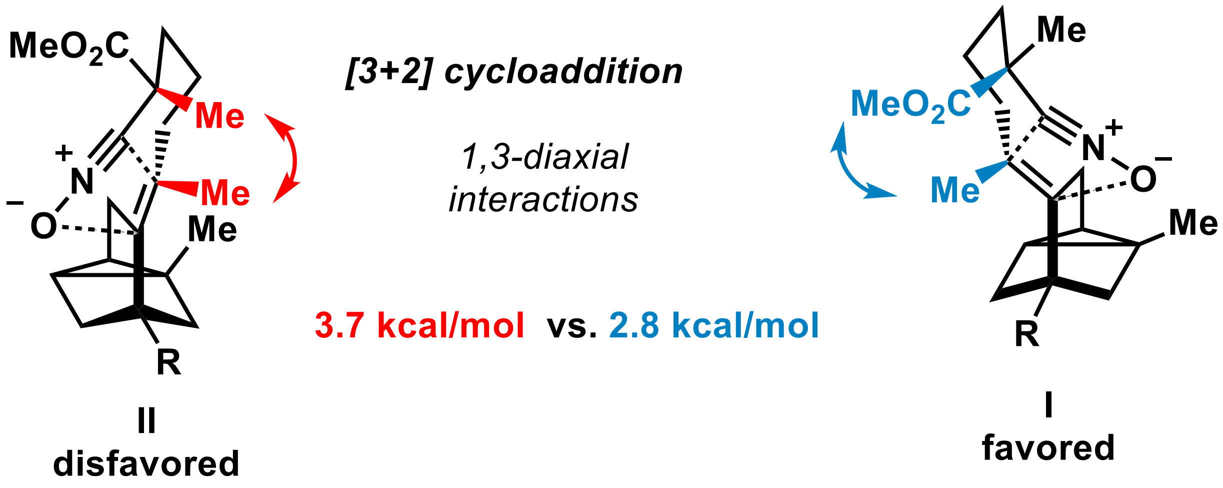
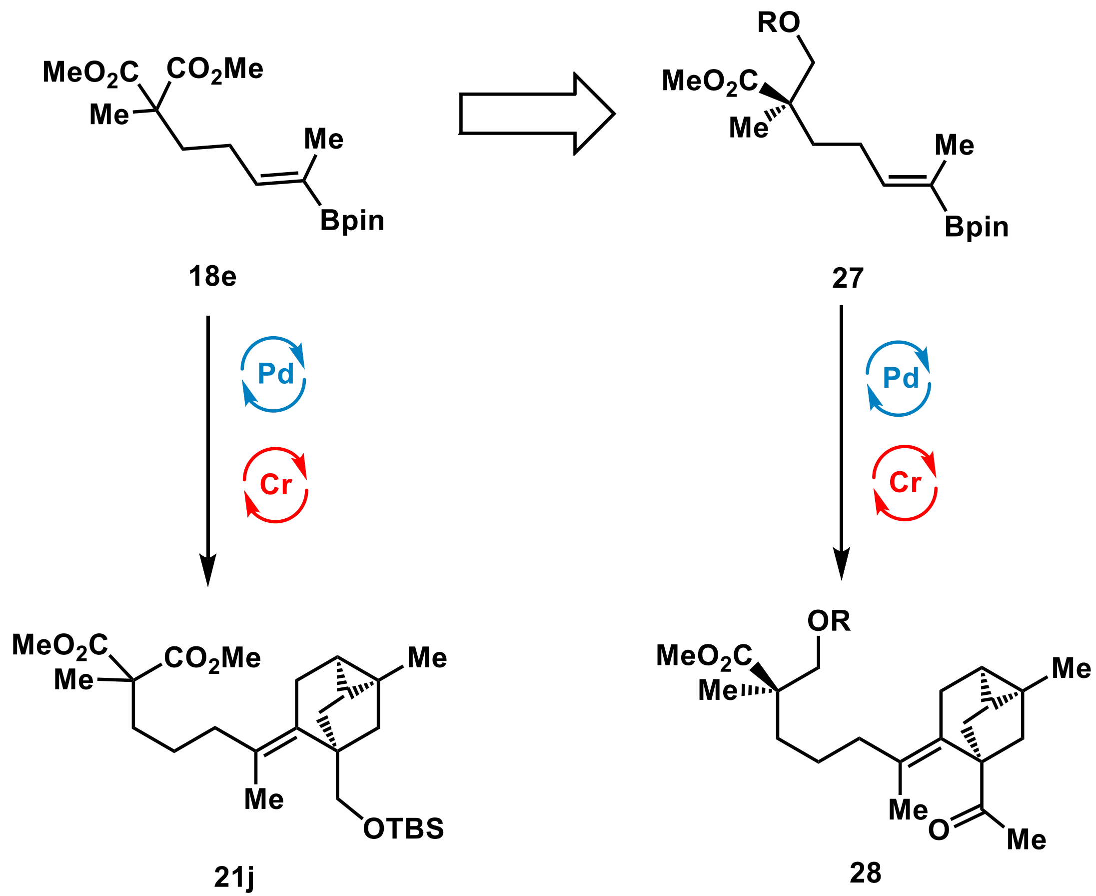
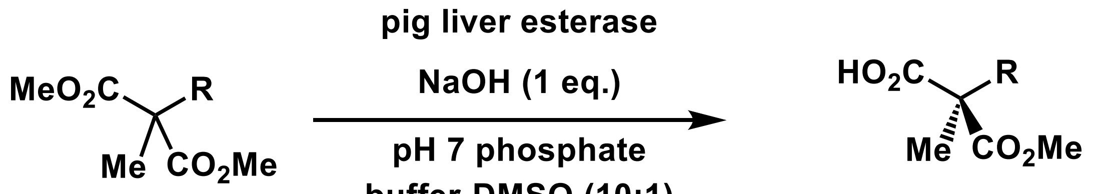


Figure 1. Putative transition states for nitrile oxide cycloaddition

Scheme 6. Envisioned Optimization of the Route

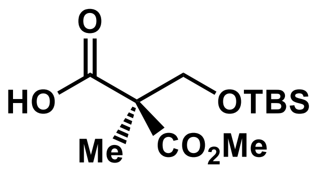


Enzymatic Desymmetrization of Malonates 29

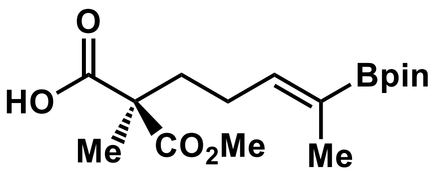


29a-f

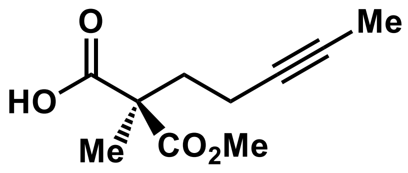
30a-f



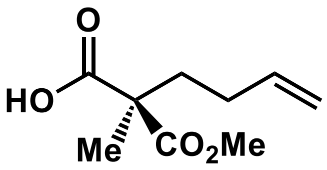
30a (39%, 95% *ee**)



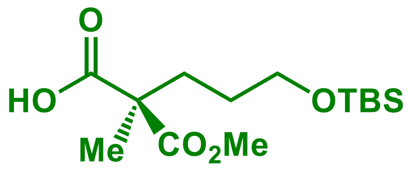
30b (9%, 75% *ee**)



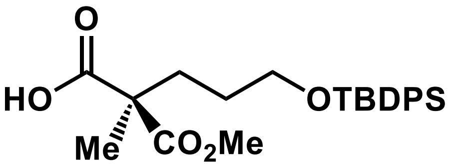
30c (74%, 20% *ee**)



30d (97%, 23% *ee**)

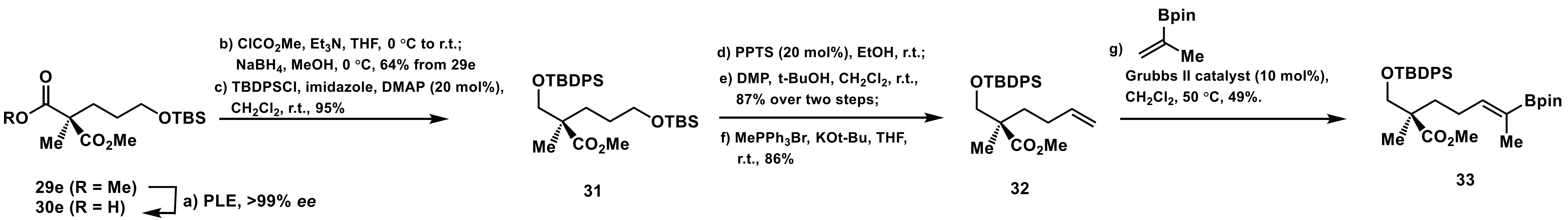


30e (67%, >95% *ee**)

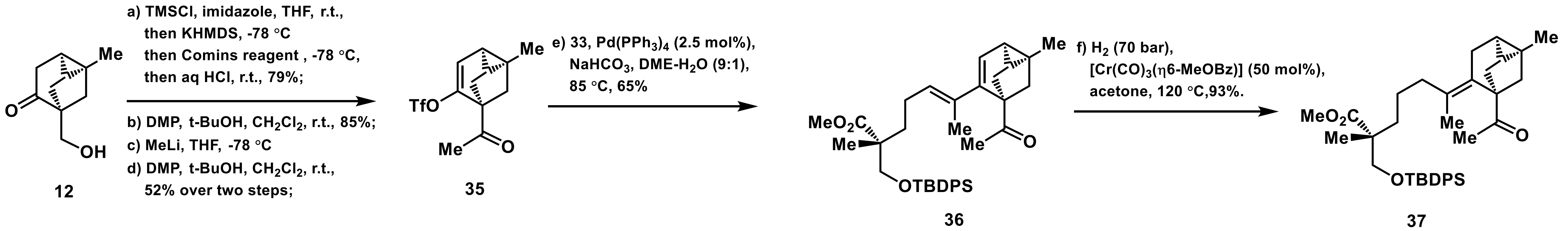


30f, not formed

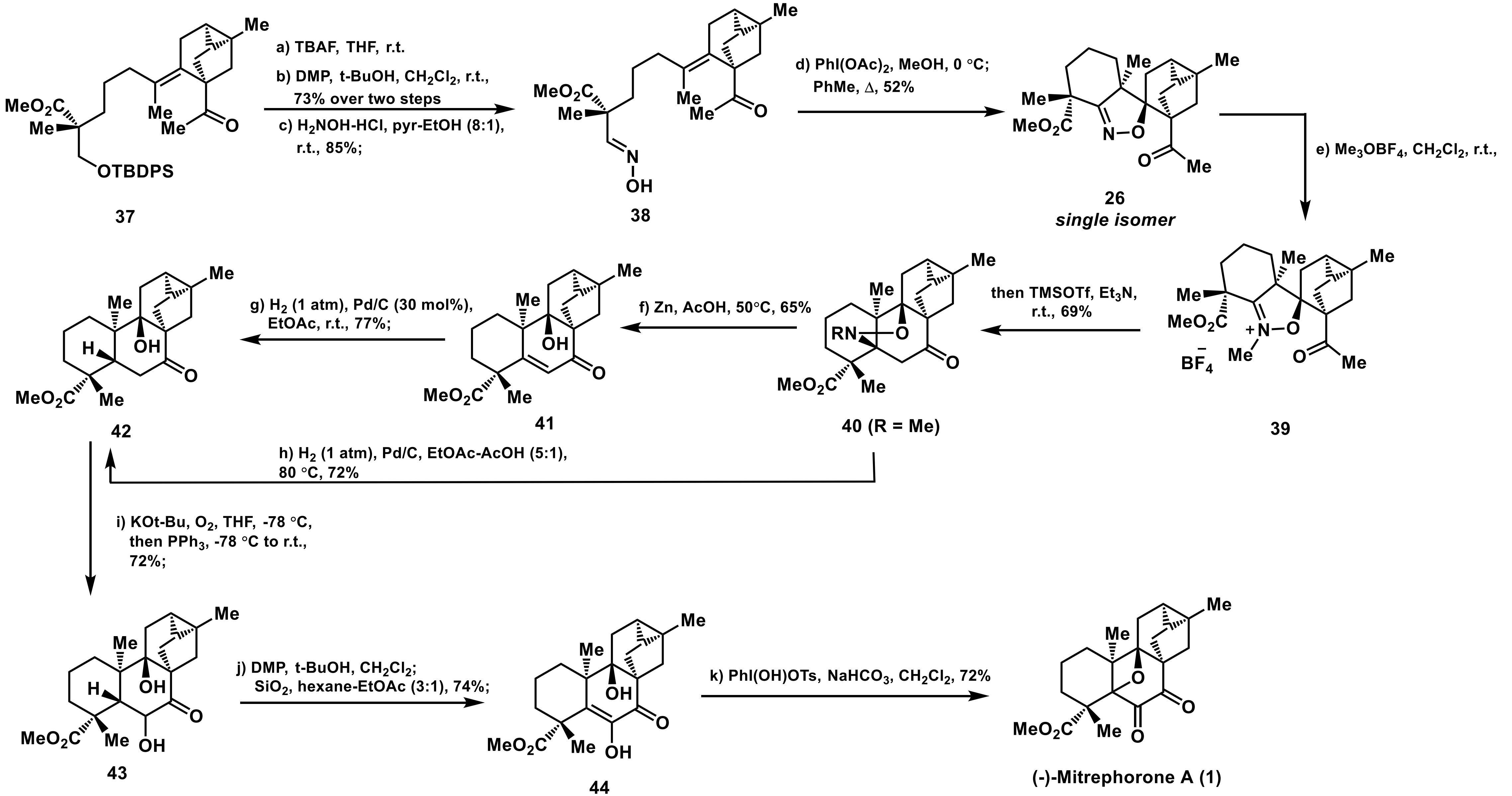
Synthesis of Vinyl Boronate 33

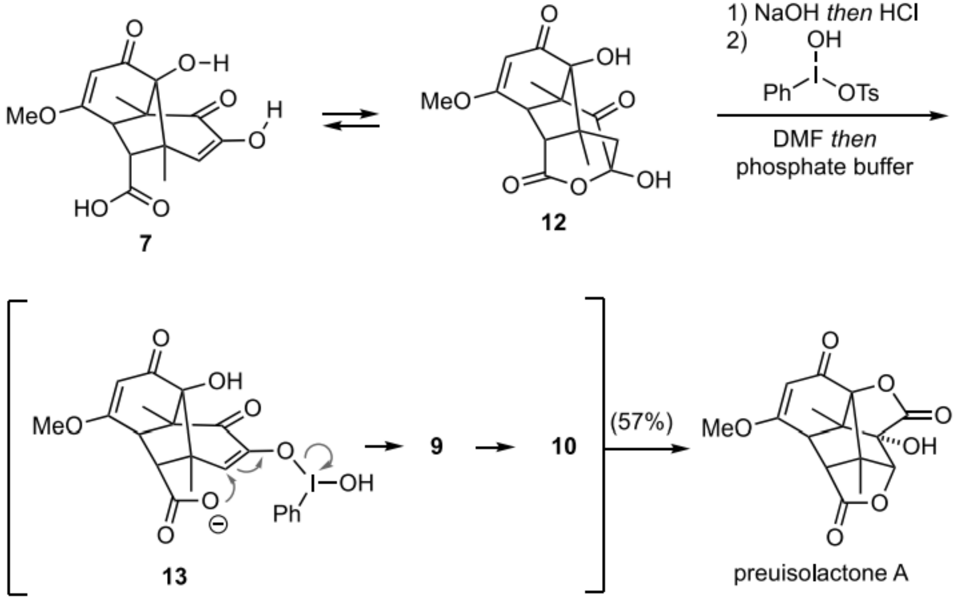


Synthesis of Tetrasubstituted Olefin 37



Synthesis of (-)-Mitrephorone via Nitrile Oxide Cycloaddition





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