Inherently chiral cavitands through ionic catalyst-controlled cross-coupling

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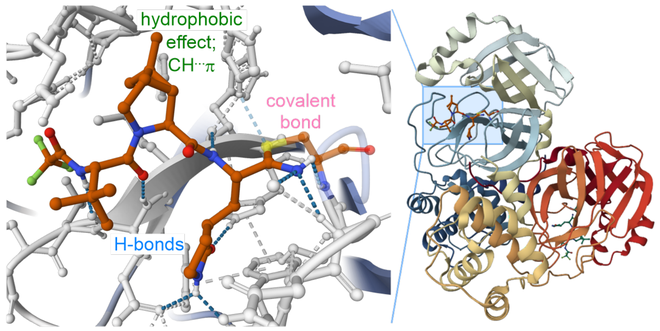
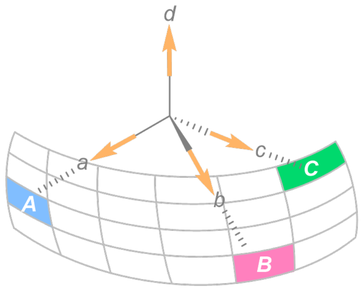
Introduction

A

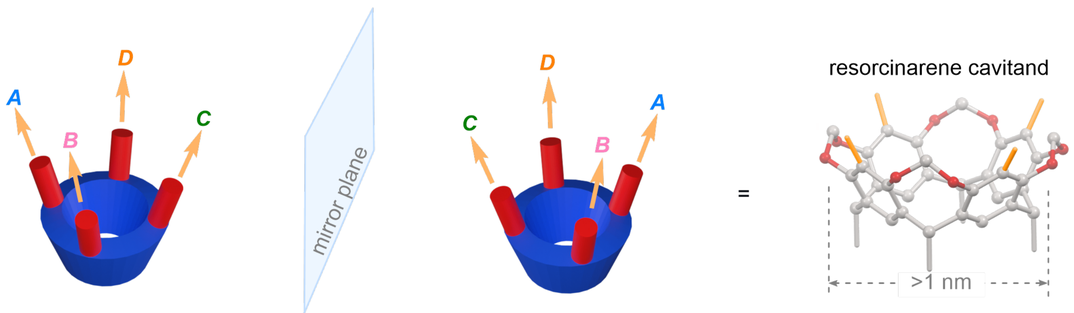


Paxlovid in complex with SARS-CoV-2 protease

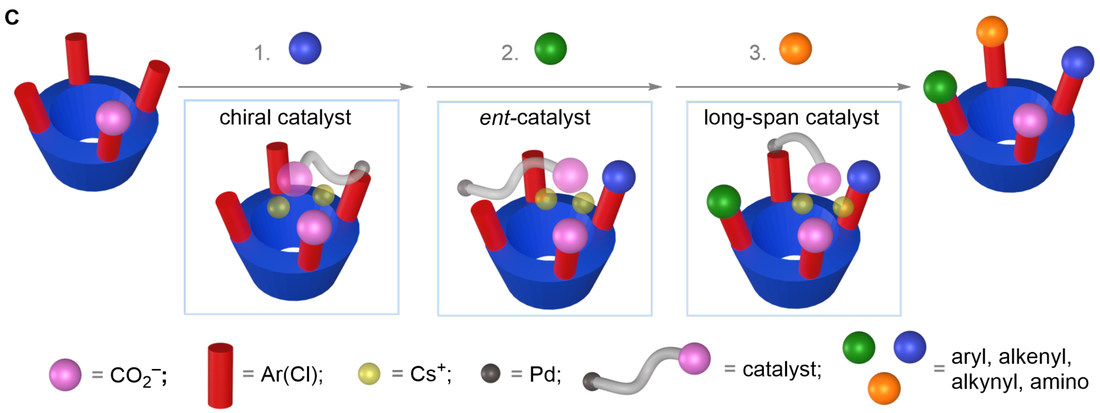


heterofunctionalized concave scaffold

B

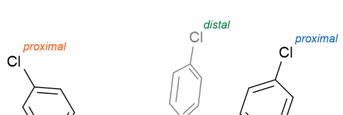


C



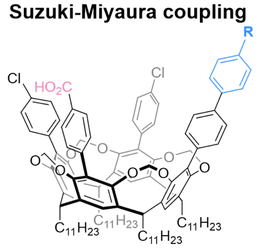
Catalyst development

Est. distance (Å) and vertical angle[a] from carboxyl of Z to	Cavitand **1** Z = CO_2H	Cavitand **2** Z = *p*-$C_6H_4CO_2H$

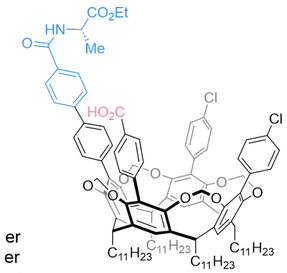


Substrate scope

Suzuki-Miyaura coupling

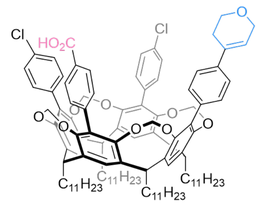


3 (R = OMe): 56%, 97.5:2.5 er
4 (R = H): 51%, 97.5:2.5 er
5 (R = CO_2Et): 41%, 94.5:5.5 er[a]
6 (R = CH_2OH): 39%, 93:7 er

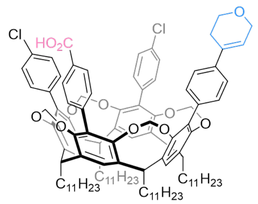


7: 58%, 94:6 dr[b,c]

Alkenyl coupling partners

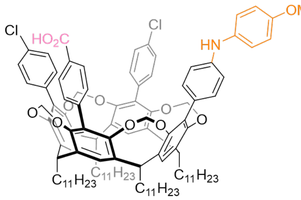


8: 39%, 92:8 er[a,c]

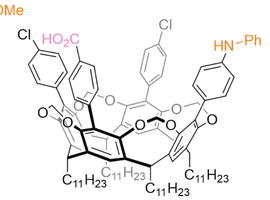


9: 38%, 93:7 er[a]

Buchwald-Hartwig amination

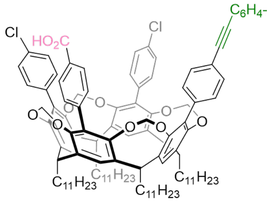


10: 29%, 89:11 er

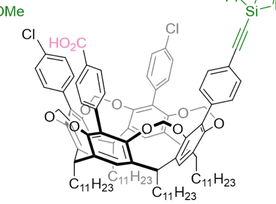


11: 41%, 94.5:5.5 er

Sonogashira coupling

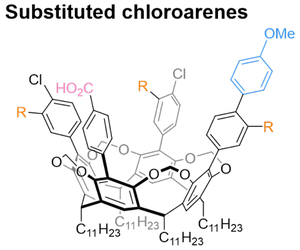


12: 43%, 97.5:2.5 er[a]



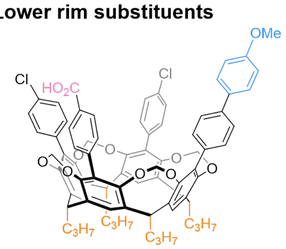
13: 34%, 95.5:4.5 er

Substituted chloroarenes

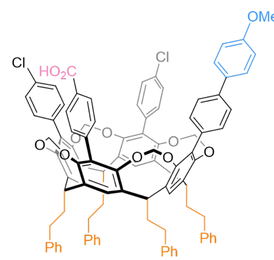


14 (R = OMe): 47%, 95:5 er
15 (R = F): 37%, 91.5:8.5 er

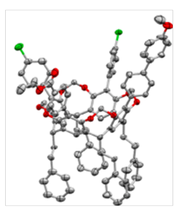
Lower rim substituents



16: 30%, 97:3 er

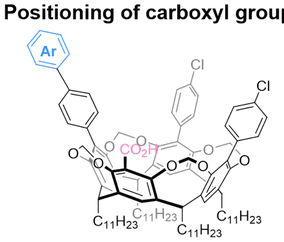


17: 44%, 96.5:3.5 er

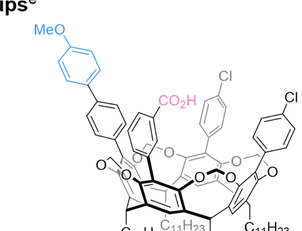


ethyl ester of **17** (x-ray[d])

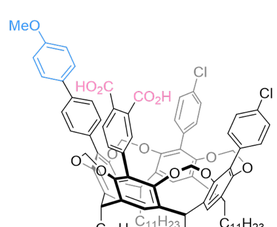
Positioning of carboxyl groups[e]



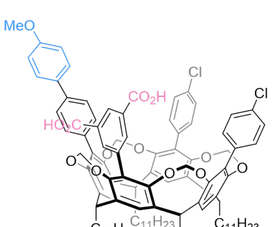
18 (Ar = *p*-C_6H_4-OMe): 48%, 90.5:9.5 er
19 (Ar = *m*-C_6H_4-CO_2Me): 64%, 90:10 er



20: 50%, 93:7 er



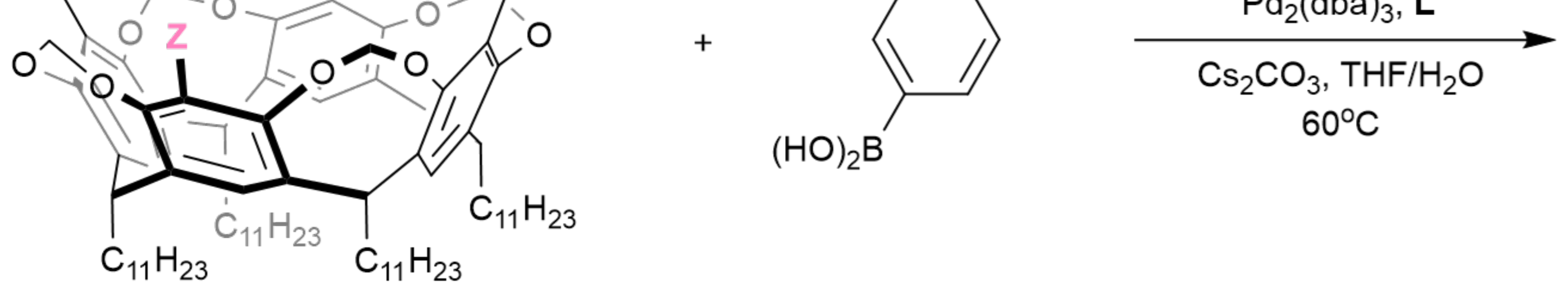
21: 41%, 94:6 er



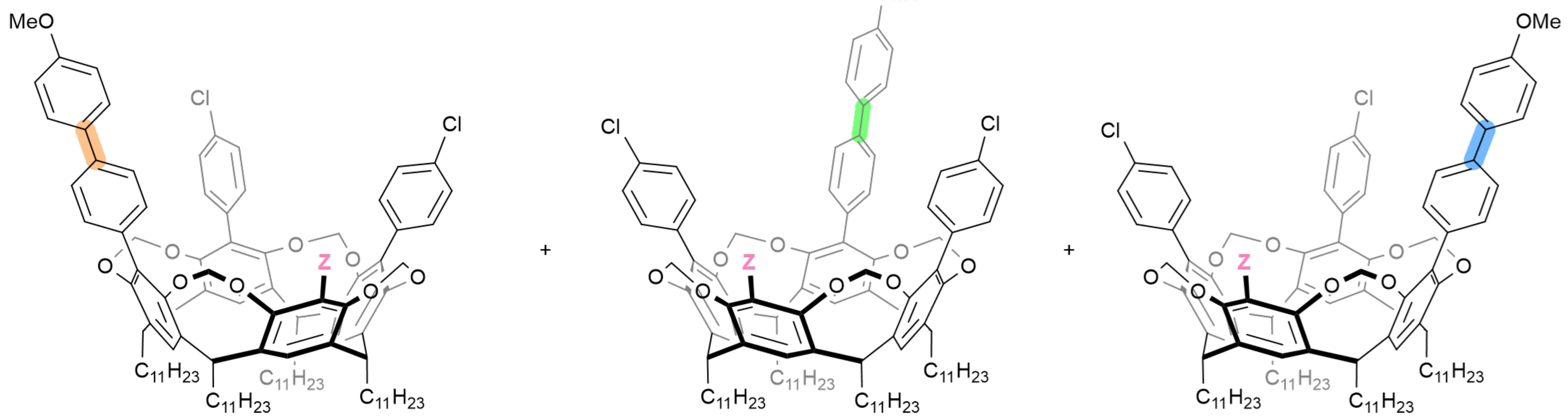
22: 39%, 90.5:9.5 er

Access ABCD-type cavitands

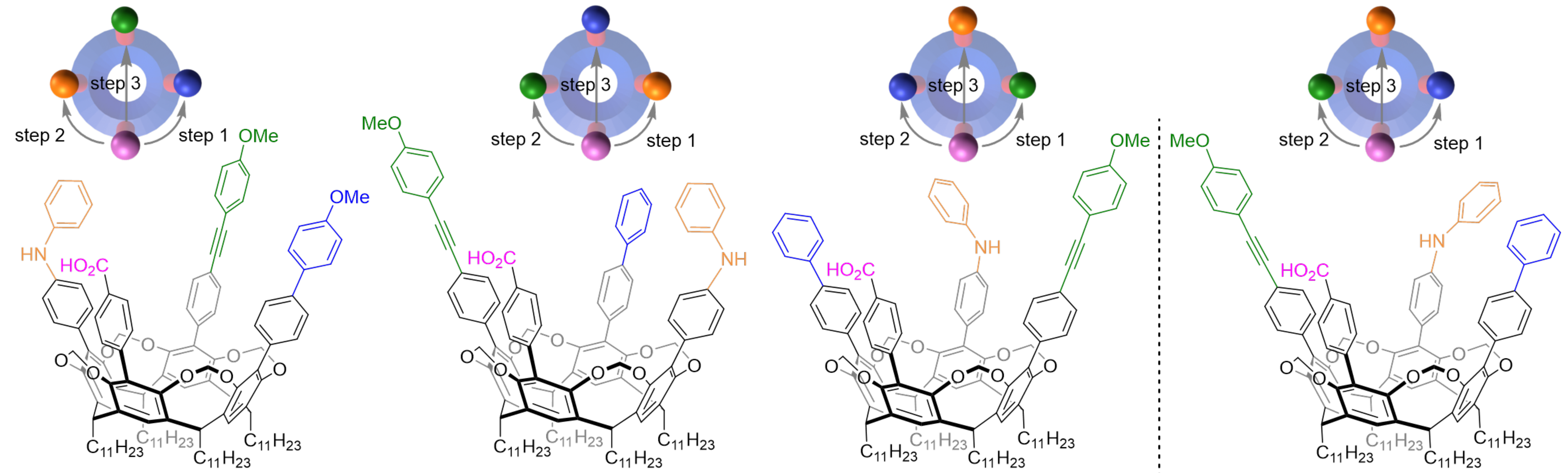
proximal Cl	9.0 (27°)	9.7 (0°)
distal Cl	12.1 (19°)	13.6 (0°)
plane defined by 3 Cl	3.6	0



1 and **2**



A **B** *ent*-**A**



24: 34% overall yield 98.5:1.5 er

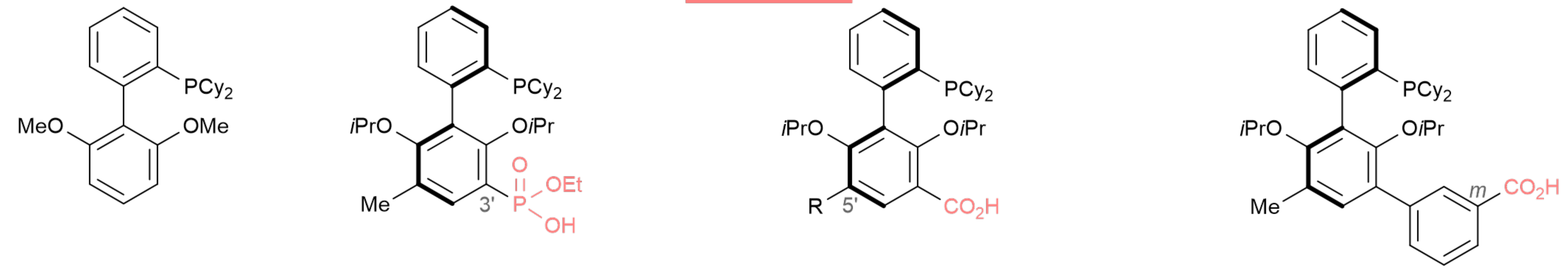
26: 16% overall yield 95.5:4.5 er

28: 16% overall yield, 99:1 er

ent-**28**: 14% overall yield 2.5:97.5 er

A. Cavitand **1** (Z = CO_2H) as substrate

Site-selectivity

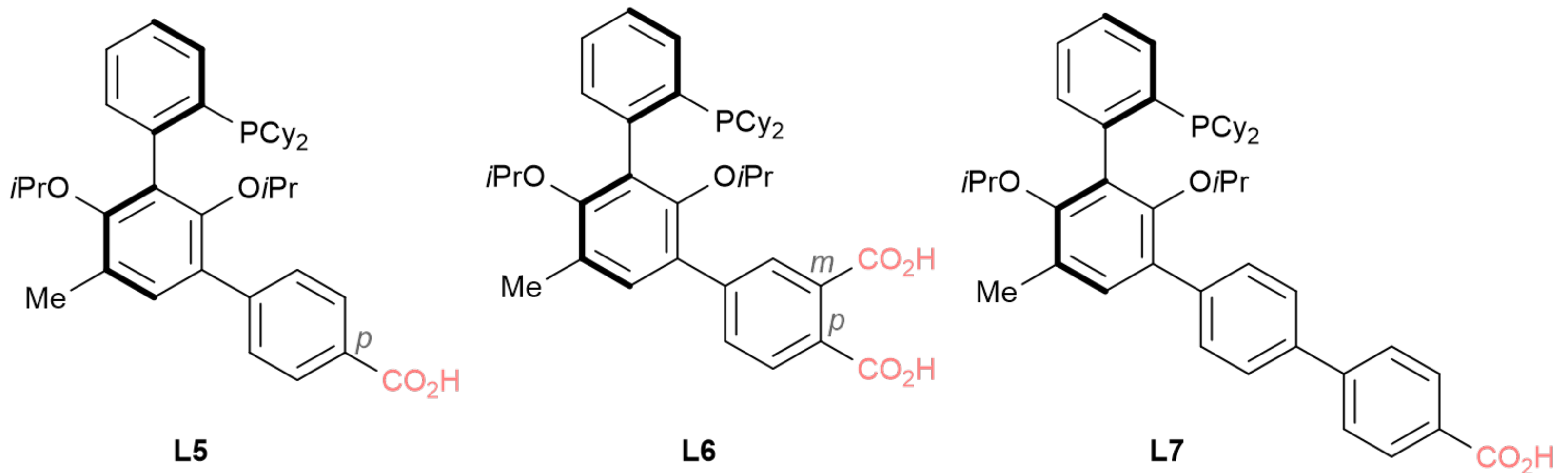


SPhos <5%

L1 20%, 6.1:1 rr, 59:41 er

L2 (R = Me): 42%, 11:1 rr, 57:43 er
L3 (R = Ph): 24%, 6.1:1 rr, 58:42 er

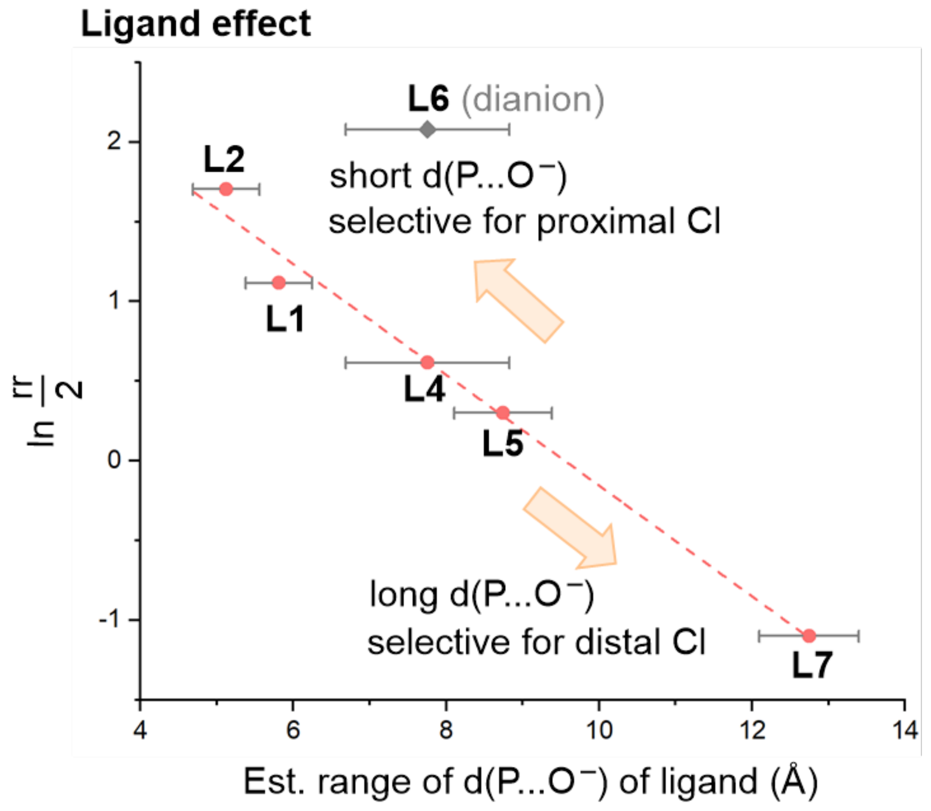
L4 41%, 3.7:1 rr, 52:48 er



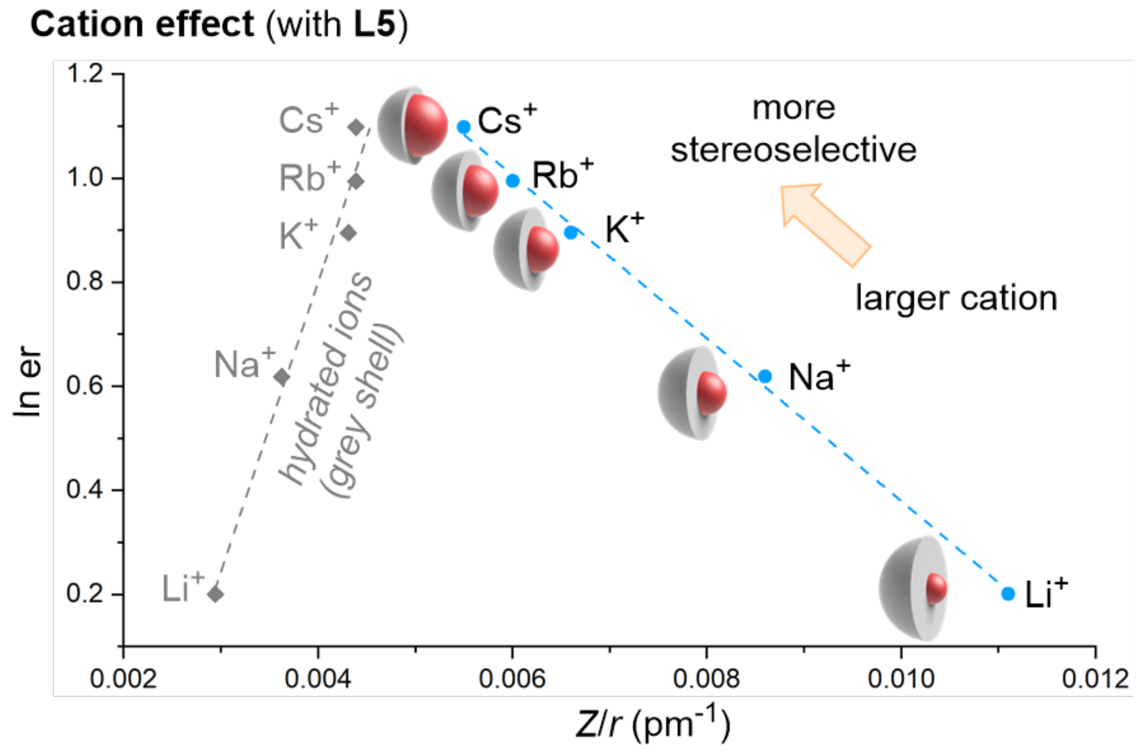
L5 45%, 2.7:1 rr, 25:75 er

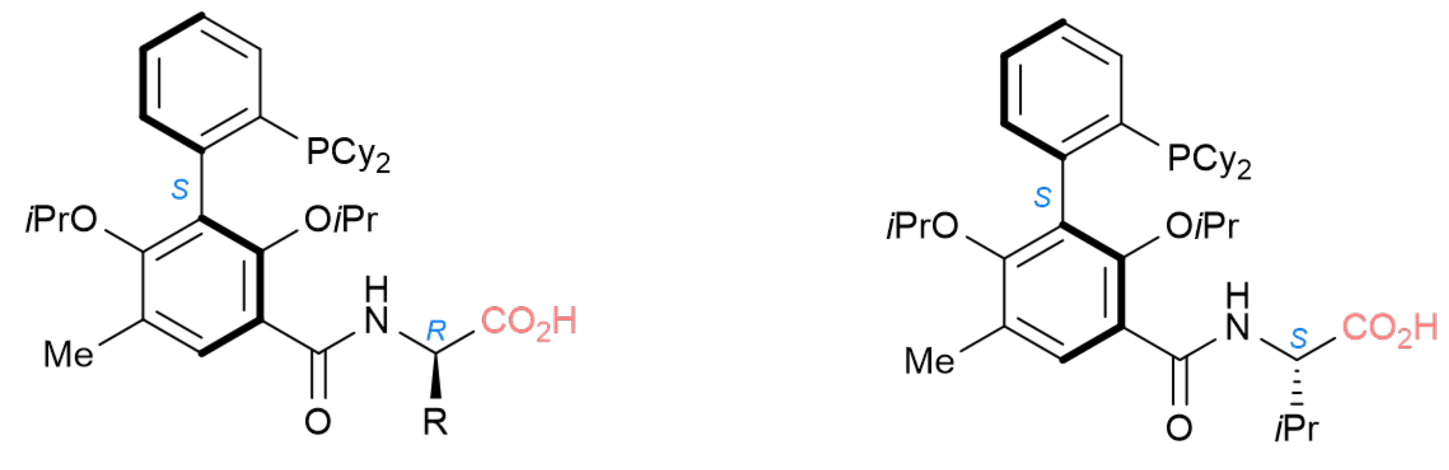
L6 62%, 16:1 rr, 41:59 er
(*rac*-**L6** used for preparation of *rac*-product markers)

L7 (long-span ligand)
49%, 1:1.5 rr, 43:57 er
52%, 1:2.0 rr, 38:62 er (2-MeTHF)



Stereoselectivity

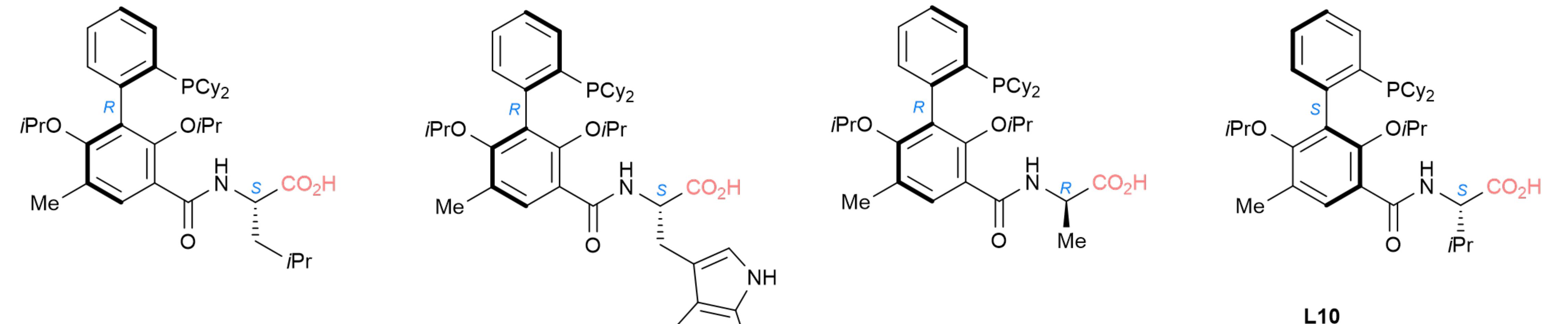




L8 (R = *i*Pr): 49%, 16:1 rr, 81:19 er
L9 (R = *i*Bu): 47%, 10:1 rr, 82:18 er
57%, >30:1 rr, 90.5:9.5 er (in 2-MeTHF)[a]

L10 30%, 3.7:1 rr, 71:29 er

B. Cavitand **2** (Z = *p*-$C_6H_4CO_2H$)



ent-**L9** 38%, 16:1 rr, 67:33 er

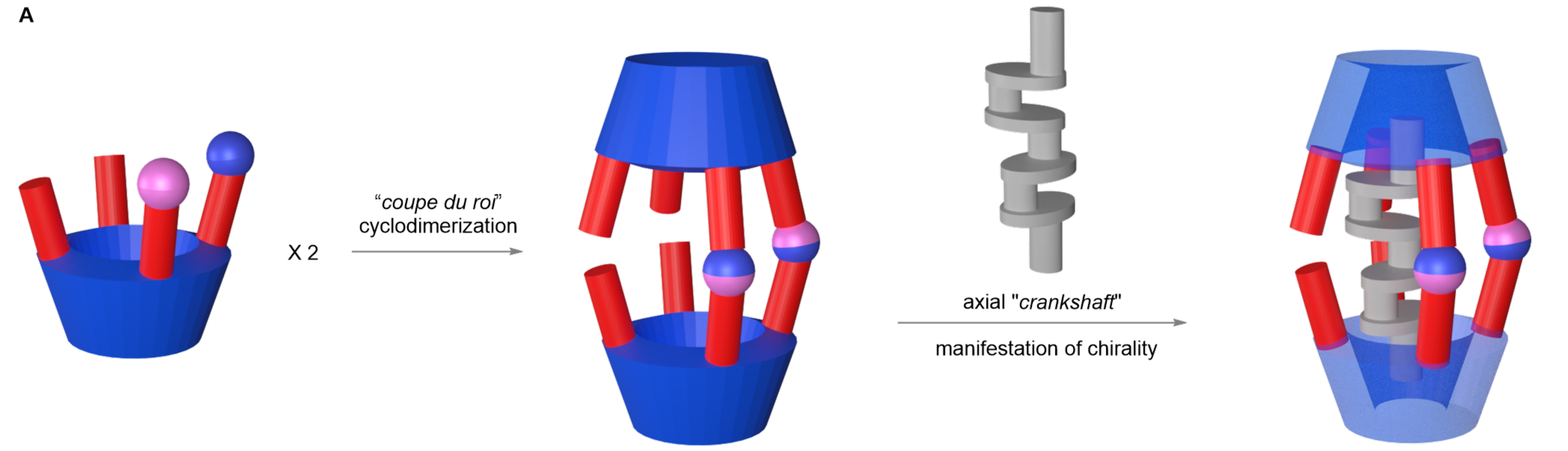
L11 43%, 5.5:1 rr, 26:74 er

L12 15%, 5.2:1 rr, 56:44 er

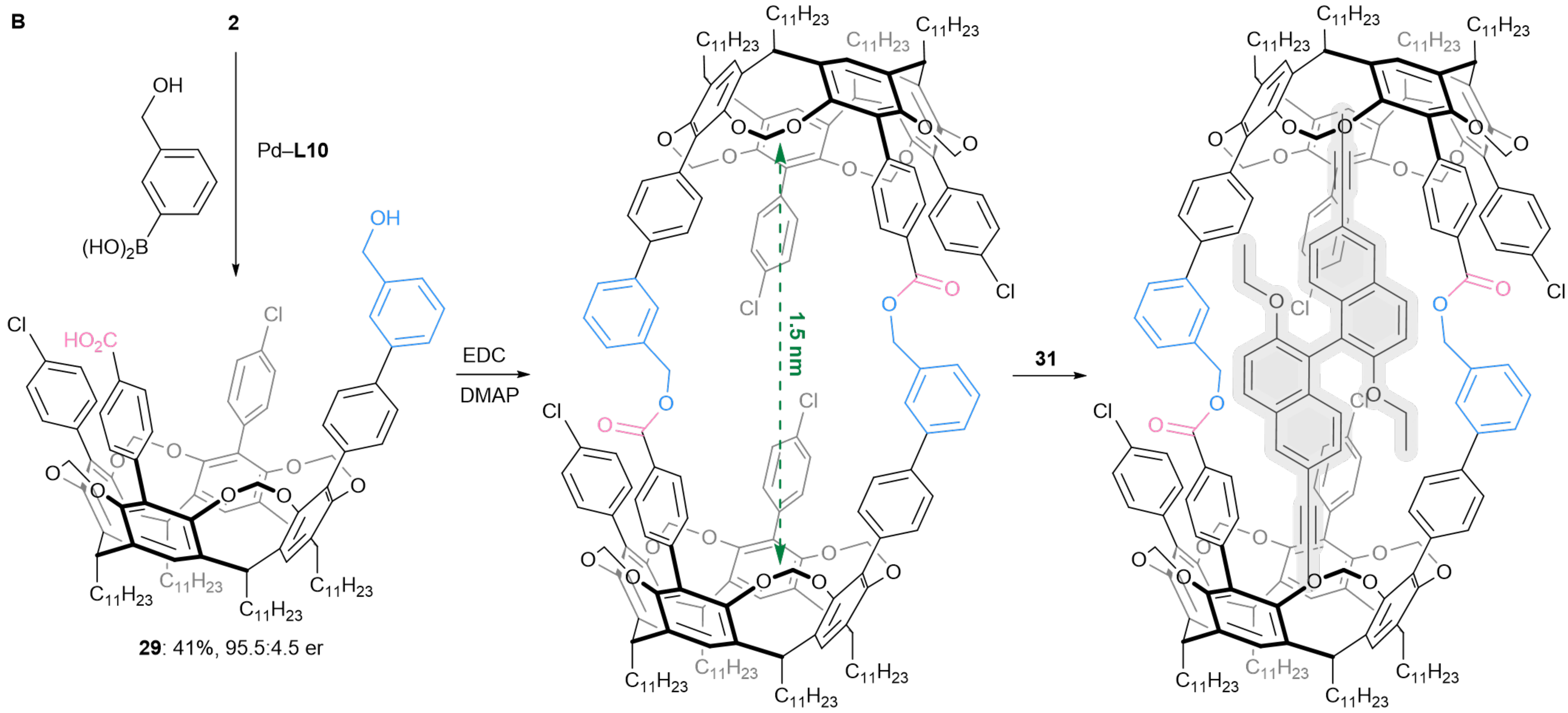
L10 50%, 11:1 rr; 94:6 er
58%, >30:1 rr, 97.5:2.5 er (in 2-MeTHF)

Molecular encapsulation and chiral recognition

A



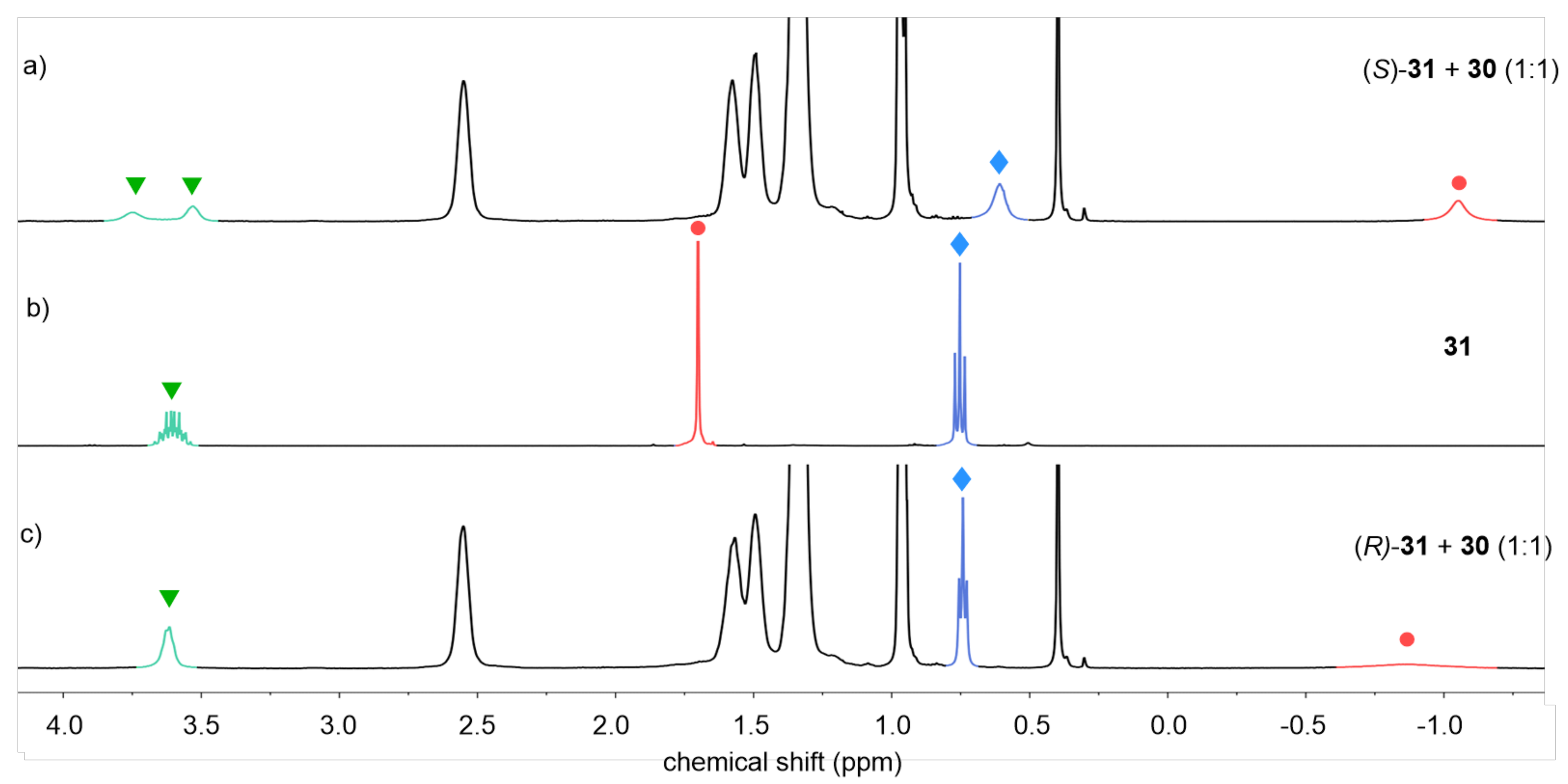
B

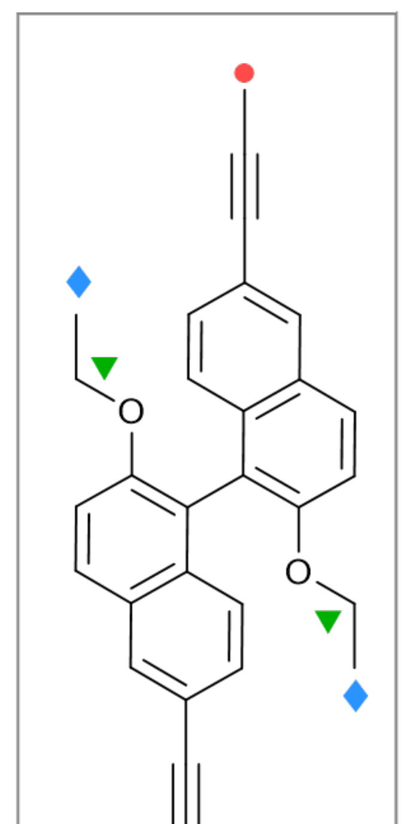


29: 41%, 95.5:4.5 er

30: 44%, >99:1 er

C





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Li, M.; Ho, C.K.S.; On, I.K.W.; Gandon, V.; Zhu, Y. *Chem.* **2024**, *10*, 3323 -3341. DOI: 10.1016/j.chempr.2024.06.012.