Enantioselective Pd-Catalyzed Trimethylenemethane Cycloadditions of All-Carbon 1,4-Dipoles

**Significance:** Trost and co-workers report the asymmetric syntheses of all-carbon chiral cyclohexanes and spiro[2.4]heptanes using palladium-catalyzed cycloadditions of aliphatic 1,4-dipoles. Using various phosphoramidite and diaminophosphite ligands, several biologically relevant scaffolds were generated in good regio-, diastereo- and enantioselectivity. The synthetic utility was demonstrated through gram-scale syntheses of each scaffold, and derivatizations included the ozonolysis and hydrolysis reactions shown.

**Comment:** Upon scale up, the palladium and ligand loading could be decreased to 2 and 4 mol%, respectively, and the cyclohexane products were formed with higher regioselectivity than the spirocycles. Interestingly, a resonance effect between the pyridine nitrogen and palladium cation center was found to be necessary for the examples with heterocyclic arenes as the second electron-withdrawing group.

**Selected examples:**

- 94% yield, 87% ee, dr > 15:1
- 64% yield, 90% ee, dr = 5.3:1
- 80% yield, 91% ee, dr = 7.1:1
- 91% yield, 43% ee, dr = 14:1

**Synthetic application:**

- 92% yield
- 86% (1 mmol scale) 92% ee, dr > 15:1

**Failed examples:**

- 86% (1 mmol scale) 92% ee, dr > 15:1