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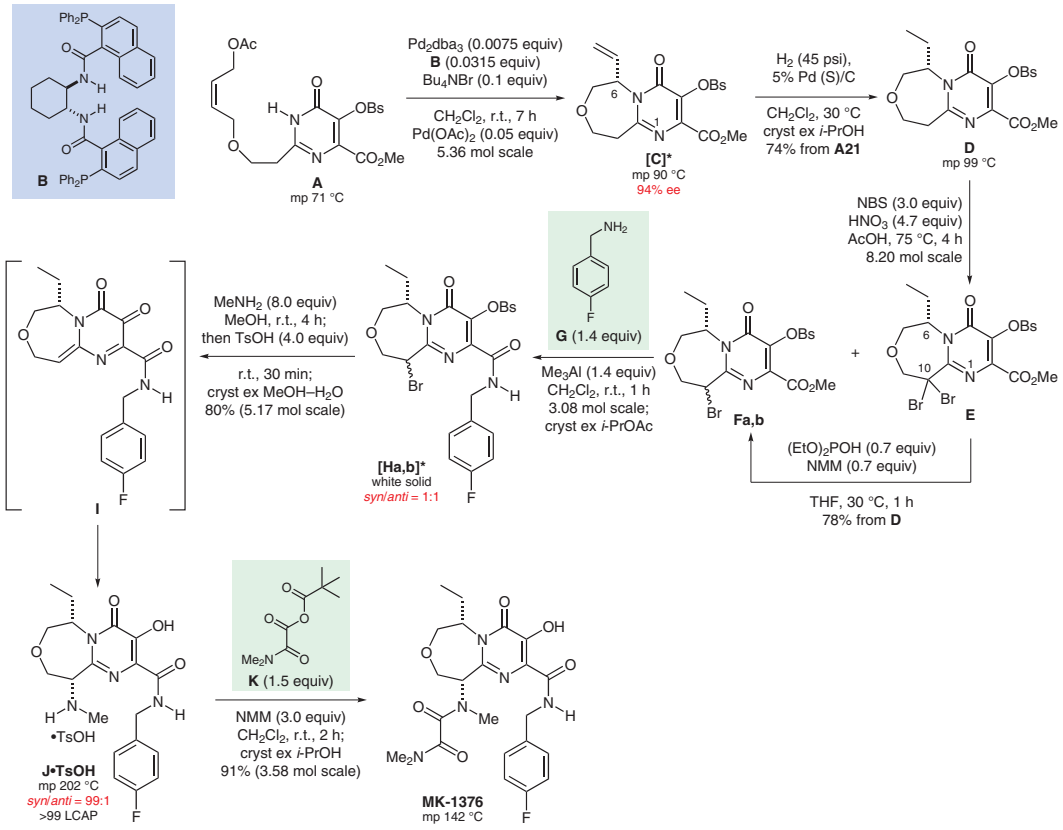
Synthesis of Fused Oxepane HIV integrase Inhibitor MK-1376
Synthesis **2020**, *52*, 3378–3388, DOI: 10.1055/s-0040-1707994.

Synthesis of HIV Integrase Inhibitor MK-1376



Significance: MK-1376 is an HIV integrase inhibitor that is of interest for the treatment of AIDS. The key step in the synthesis of MK-1376 is the Trost palladium-catalyzed asymmetric π-allylation reaction that installed the stereogenic center at C-6 in the 1,4-oxazepane ring of **C**. Prolonged reaction times led to erosion of ee from reversible ring closure. This is the first example of reversibility in a π-allylation reaction. The epimerization processes were suppressed by addition of 1.5 mol% palladium acetate prior to workup.

Comment: Introduction of the stereogenic center at C-10 was accomplished by reaction of methylamine with the amides **Ha,b** (*syn*/*anti* = 1:1) that gave the *syn*-isomer **J** (*syn*/*anti* = 97:3), independent of the original stereochemistry at C-10, consistent with the diastereoselective addition of methylamine to quinone methide intermediate **I**.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

MK-1376

HIV integrase inhibitor

π-allyl alkylation

palladium catalysis

quinone methide

Synfact of the Month