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Functional-Group-Tolerant, Nickel-Catalyzed Cross-Coupling Reaction for Enantioselective Construction of Tertiary Methyl-Bearing Stereoisomers

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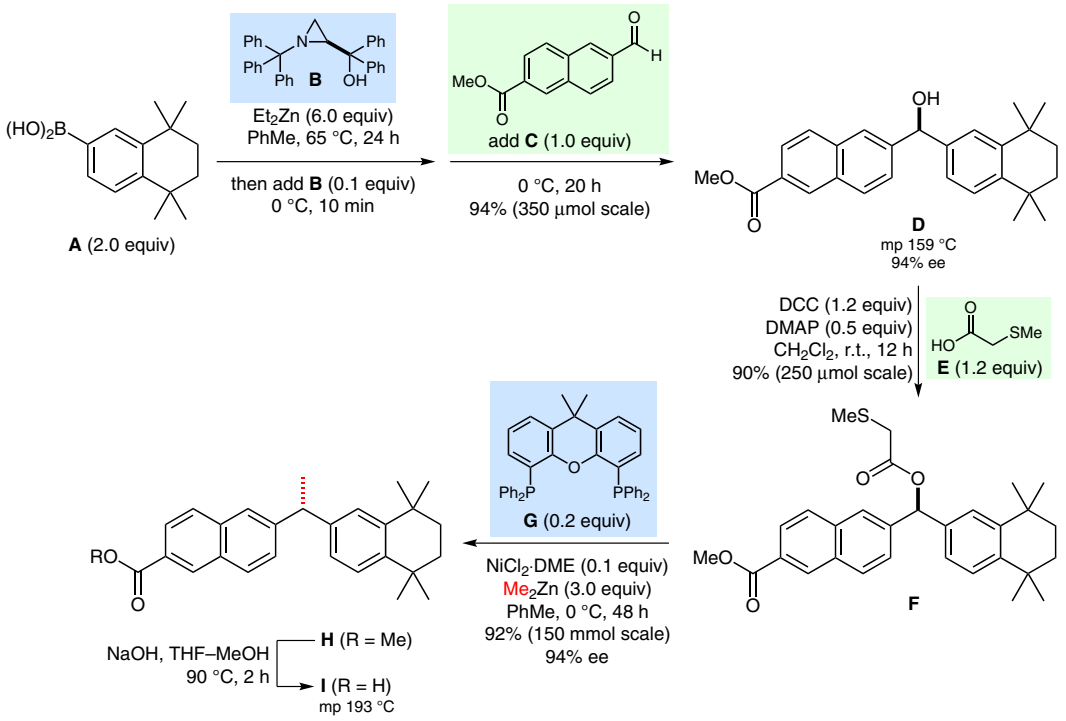
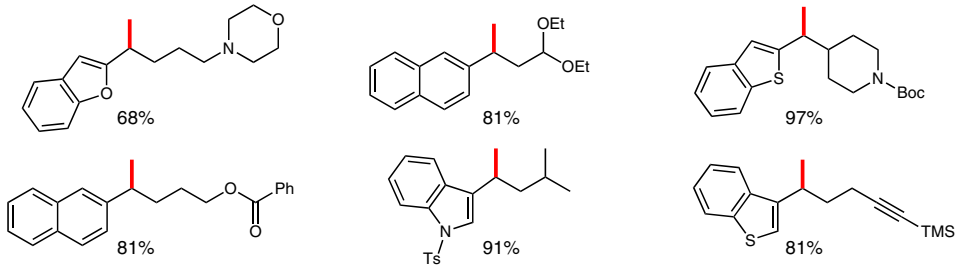
Synthesis of a Retinoic Acid Receptor Agonist



Scope of the Negishi alkyl–alkyl cross-coupling



Significance: The target molecule **I** is a retinoic acid receptor γ (RARγ) agonist that is of interest for the treatment of acne, psoriasis and melanoma. The synthesis depicted features the first nickel-catalyzed stereospecific Negishi alkyl–alkyl cross-coupling reaction of secondary benzylic α-(methylthio)acetate esters with dimethylzinc.

Comment: The mild reaction conditions are compatible with a variety of functional groups including alkenes, protected alkynes, acetals, and esters. Heterocycles, amines, and imides are also well tolerated. Cross-coupling with diethylzinc is also possible but the reaction is more complex owing to additional competitive reaction pathways.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

retinoic acid receptor agonist

nickel-catalyzed cross-coupling

α-(methylthio)-acetate esters

dimethylzinc