Creation of alkyl substituent in α-position of methylene ketones: efficient synthetic toolbox

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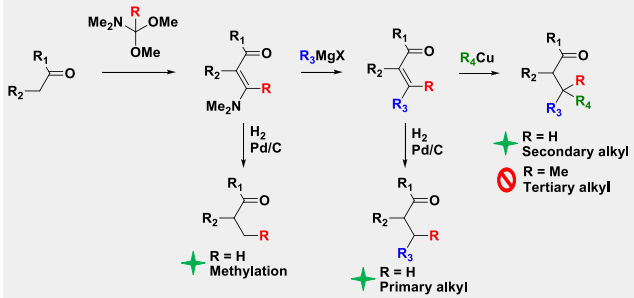
Background and synthetic strategy

Diverse primary and secondary alkyls were introduced to cyclic ketones via synthesis of enaminone (step one) with subsequent treatment with organomagnesium (step 2) and organocopper (step 3) reagents. This “chemical constructor” approach allows to introduce a large number of α-substituents using a limited set of reagents like numerous buildings can be constructed from a limited set of Lego bricks.

“Chemical constructor” approach

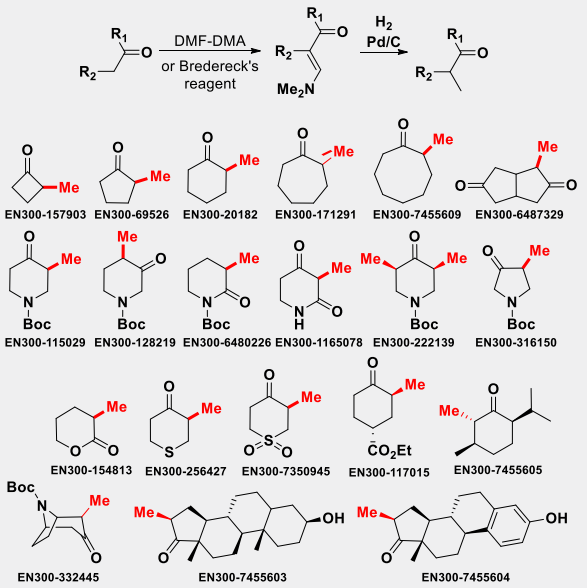


Scope and Limitations of the Method

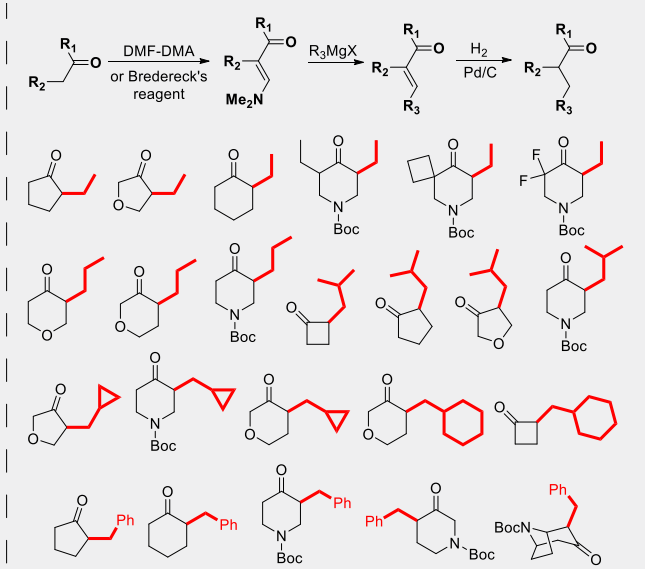
- **Methylation** with DMF-DMA or Bredereck’s reagent followed by H_2 /Pd reduction of the resulting enaminone (23 examples);
- Introduction of a **primary alkyl** with DMF-DMA or Bredereck’s reagent followed by Grignard reaction with the resulting enaminone (6 examples of Grignard reagents, 15 ketones) and subsequent H_2 /Pd reduction;
- Introduction of a **secondary alkyl** with DMF-DMA or Bredereck’s reagent followed by Grignard reaction with the resulting enaminone and subsequent modification with an organocopper reagent;
- High **selectivity** for less hindered α-position was determined.
- Limitations for the introduction of a **tertiary alkyl** were shown.

Research Results & Representative Examples

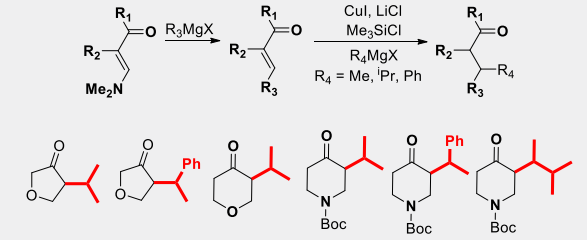
Methylation



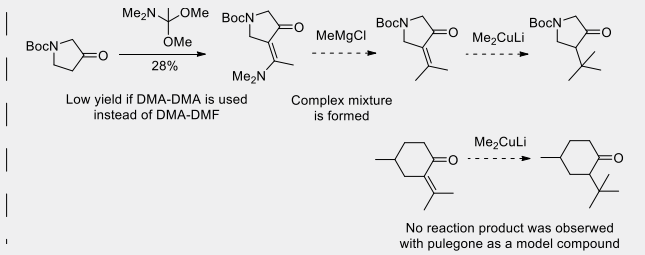
Primary alkyls



Secondary alkyls



Limitations for tertiary alkyl introduction



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Results have been published as

Selective α-Methylation of Ketones. *Frolov A.. I. et al., J. Org. Chem.* **2021**, *86*, 7333–7346.
https://doi.org/10.1021/acs.joc.1c00148
One more paper is underway