Recent Advances in Difluorocyclopropanation of alkenes using Ruppert–Prakash reagent.

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**Introduction and Aim**

Modern medicinal chemistry widely exploits two structural motifs to improve physico-chemical characteristics of the compounds: fluorine atoms and small rings. The best way for generating the smallest one example of them, difluorocyclopropane, is difluorocyclopropanation of alkenes by difluorocarbene or its synthetic analogues. The Ruppert–Prakash reagent (CF$_3$SiMe$_3$) is one of the most convenient difluorocarbene equivant to achieve that transformation. Nevertheless, it was studied a bit to date, mostly with non-functionalized substrates.

We optimized the reaction conditions and elaborated the methodology for using this reagent for a wide set of substrates called “slow addition protocol”. In a series of works, we described the synthesis of various functionalized difluorocyclopropanes—valuable building blocks for medicinal chemistry in a multigram scale by the evaluation of this protocol. The scope and limitations were significantly enlarged to electron-deficient substrates, the yields were extremely increased and the conditions was strongly optimized.

**Process Optimization & Scope**

![Diagram showing conversion and relative reactivity of substrates]

**Results**

- Relative reactivity of the substrates
- Conversion, %
- Temperature, °C

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**References**