FLUOROUS TAGS IN ORGANIC CHEMISTRY

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FLUOROUS TAGS

Highly fluorinated molecules easily separate from both aqueous and organic molecules, forming their own distinct phase. Fluorous tags, long fluorocarbon chains attached to a molecule of interest through a spacer, can therefore be used to separate tagged molecules from non-tagged molecules using either fluorous liquid-liquid extractions or fluorous solid phase extractions (F-SPE). Fluorous tags can be used to separate product from crude reaction mixtures by tagging either the substrate or the reagents. This is especially useful in reactions where separation of the product from other materials in the crude reaction mixture or recovery of an expensive catalyst is particularly difficult.

USES OF FLUOROUS TAGS

The Mitsunobu Reaction

The Mitsunobu reaction is widely used in synthesis due to its broad scope, stereospecificity, and mild conditions. However the separation of the product from the spent reagents usually requires difficult and tedious chromatography that must be optimized for each substrate. Fluorous derivatives of both the azodicarboxylate and triarylphosphine reagents coupled with F-SPE have been shown to greatly simply the purification.[1] While the first generation reagents were found to be not as reactive and struggled to produce adequate yields on more challenging substrates, the second generation reagents improved reactivity and made the fluorous reagents competitive with their non-fluorinated counter parts, providing a practical solution to a limitation of the Mitsunobu reaction.[2]

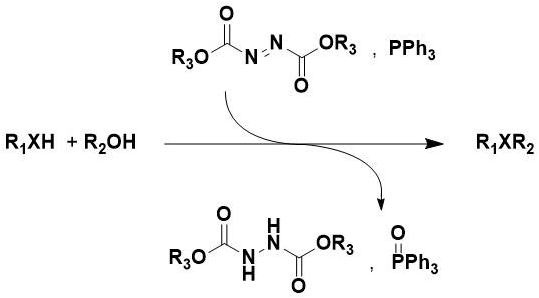

Figure 1 The Mitsunobu Reaction and byproducts that must be separated

Recycling of Fluorous Catalysts

Rhodium catalysts tends to give higher yields and better selectivites for hydroformylation than other metals, but the expense and difficulty of recovering the rhodium catalyst limits its use. Using fluorous tagged phosphine ligands have been shown to allow not only allow the recovery of the catalyst,

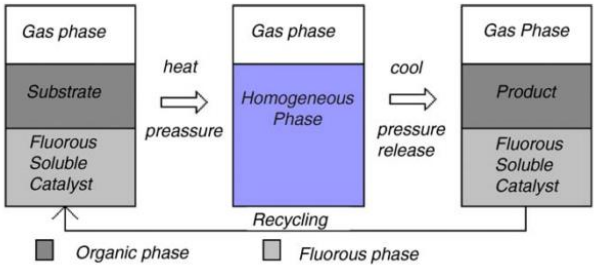

Figure 2 Recycling of hydroformylation catalyst using fluorous tags and solvents

but also the automation of the reaction and recycling process (**Fig 2**). The Hope group utilized fluorous tagged phosphine, fluorous solvent, and a rhodium catalyst to perform the hydroformylation of 1-octene in a continuous flow reactor that constantly recycled the solvent, the ligand, and the catalyst.[3] While some leaching of both catalyst and ligand was observed, they were able to run the machine for 20 hours and observed more than 15,500 turn overs of the catalyst during that time, with an average of 750 turnovers per hour.

Total Synthesis of Dictyostatin and Three Stereoisomers

Dictyostatin is a potent microtubule stabilizer that has been shown to have anticancer activity. Due to members of the same family of molecules tolerating stereochemical changes at positions 6 and 7, the Curran group wanted to make all possible stereoisomers of these two positions. (**Fig 3**) By installing silyl protecting groups with differing lengths of fluorous tags on each diastereomer, the Curran group was able to complete a total synthesis of all four diastereomers in one pot.[4] They then utilized fluorous prep-HPLC to separate the compounds based on the number of fluorines in the tag; deprotection then afforded each of the diastereomers. Testing in a human ovarian carcinoma cell line showed that 6-*epi*-dictyostatin was 4 times more potent than dictyostatin.

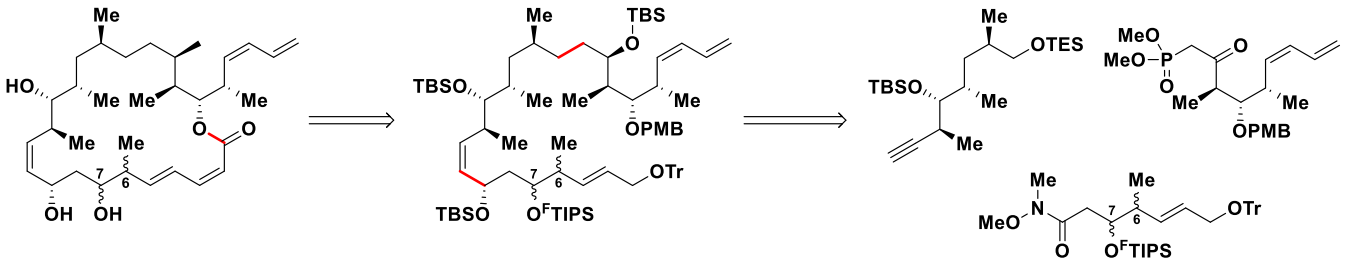

Figure 3 Retrosynthesis of Dictyostatin and isomers

References

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2.) Dandapani, S.; Curran, D.P.; *J. Org. Chem.*, **2004**, *69*, *8751*
3.) Perperi, E.; Huang, Y.; Angeli, P.; Manos, G.; Mathison, C.R.; Cole-Hamilton, D.J.; Adams, D.J.; Hope, E.G.; *Chem Eng Sci*, **2004**, *59*, 4983
4.) Fukui, Y.; Bruckner, A.M.; Shin, Y.; Balachandran, R.; Day, B.W.; Curran, D.P,; *Org Lett*, **2006**, *8*, 301