SYNLETT
Spotlight 422

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Triflic Acid

Compiled by Nicolas Gigant

Nicolas Gigant was born in 1986 in Vagney, France. He graduated from the National Graduate School of Engineering Chemistry of Lille in 2009 and received his M.Sc. in Organic Chemistry in the same year. He is currently pursuing his Ph.D. under the supervision of Professor Isabelle Gillaizeau. His research is focused on the synthesis and reactivity of cyclic enamides for the development of new methodologies giving access to motifs frequently found in 'privileged structures' or key scaffolds present in natural products or potentially bioactive compounds.

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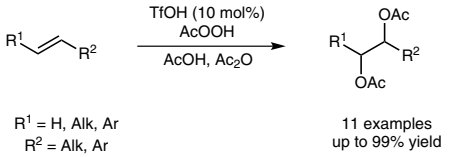
Introduction

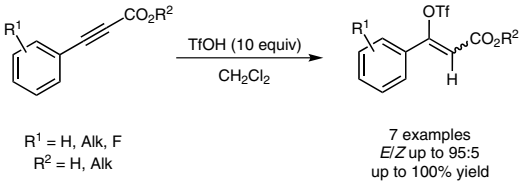
Trifluoromethanesulfonic acid (TfOH), more commonly named triflic acid, is one of the strongest Brønsted acids and well known as a 'super acid' with a pK_a of –13.6. The reagent is a colorless liquid and stable towards heating, oxidation and reduction. It was first synthesized in 1954 by Haszeldine and Kidd by oxidation of bis(trifluoromethylthio)mercury with aqueous hydrogen peroxide.[1] It is available on an industrial scale and is produced by electrochemical fluorination. Triflic acid is an effective reagent widely used in organic chemistry and especially as catalyst (historically for esterification and salt formation),[2] even if more than one equivalent is often used.[3] However, its utilization mainly includes addition to α-carbonylated alkynes,[4] hydrogenation,[5] Friedel–Crafts reaction,[6] polymerization,[7] cycloaddition,[8] deprotection,[9] initiation of cyclisation sequences,[10] and as a counterion both for iodonium salts[11] and N-heterocyclic carbenes.[12]

Abstracts

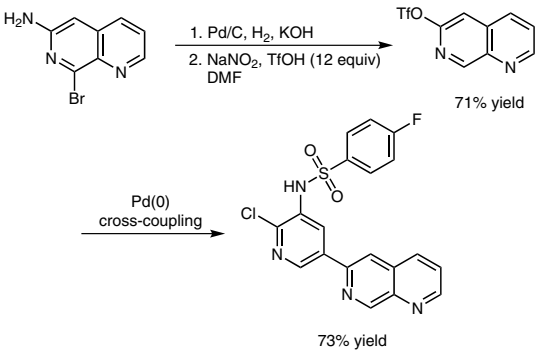
(A) *TfOH as Catalytic Reagent:*
An efficient metal-free diacetoxylation reaction of alkenes catalyzed in the presence of 10 mol% of triflic acid has been described by Gade.[3a] TfOH plays a double role in this process: it catalyzes the ring-opening of the intermediate epoxide as well as the subsequent acetylation of the hydroxyl group.



(B) *Addition to α-Carbonylated Alkynes:*
Various vinyl trifluoromethylsulfonates have been recently isolated by the addition of triflic acid to the triple bond of propynoate derivatives.[4] The stereoselectivity could be controlled by adjusting the reaction conditions. Moreover, the generated vinyl triflates are very reactive intermediates towards metal cross-coupling reactions.[13]



(C) *Synthesis of Aryl Triflates:*
Another application of triflic acid was illustrated by the synthesis of a potential medicinal agent.[14] After catalytic hydrogenation of the bromine atom, the corresponding naphthyridin was transformed by diazotization of the amine followed by a nucleophilic substitution with TfOH. The resulting aryl triflate was used in a selective Suzuki–Miyaura cross-coupling to give the desired scaffold with good yield.



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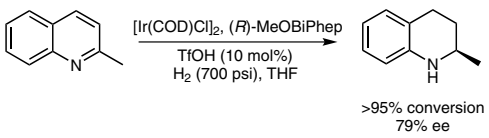
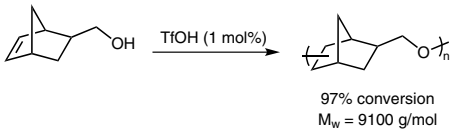
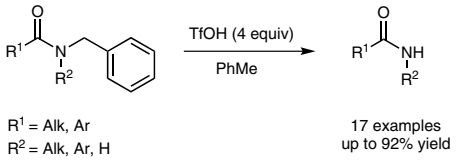
(D) *Catalytic Asymmetric Hydrogenation:*
A simple enantioselective hydrogenation catalyzed by an iridium–diphosphine complex with a catalytic amount of activator was reported by Zhou and co-workers.[5] Both the reactivity and enantioselectivity were enhanced in the presence of 10 mol% of TfOH. The complex 'piperidine·TfOH' is also efficient.



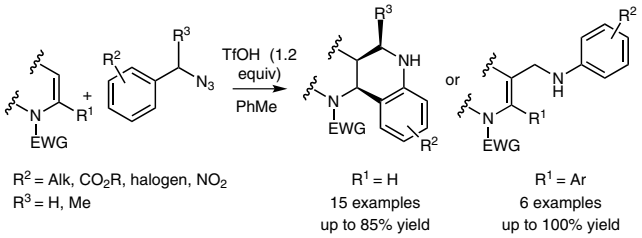
(E) *Polymerization Catalyzed by TfOH:*
Mathers et al. proposed the first polymerization method using hydroalkoxylation and hydrocarboxylation reactions catalyzed under acidic conditions.[7] In presence of triflic acid, the conversion, the weight average, and the molecular weight are improved compared to the use of H_2SO_4.



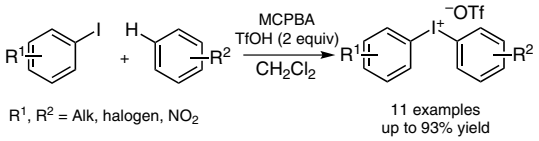
(F) *TfOH as a Deprotecting Agent:*
TfOH has been involved in a fast and convenient microwave-assisted N-debenzylation of amides with a benzyl cation as the intermediate.[9] Both secondary and tertiary amides bearing various functional groups were isolated in good to high yield. Attempts to reduce the number of equivalents of TfOH, decreased the conversion dramatically.



(G) *Domino Reaction:*
Gillaizeau and co-worker have demonstrated that triflic acid can be involved in a domino reaction for the diastereoselective synthesis of polyfunctionalized nitrogen-fused tetrahydroquinoline frameworks or 2,3-functionalized enamides.[10] The rearrangement and the formation of the iminium ion intermediate are initiated by triflic acid. Products were obtained in low yield using a substoichiometric quantity of TfOH.



(H) *Counter-ion for Diaryliodonium Triflates:*
Triflic acid has been selected for the synthesis of diaryliodonium salts. Olofsson and co-workers have developed an efficient one-pot synthesis starting from aryl iodides and arenes.[11a] The aryl iodide is oxidized by MCPBA to an iodine(III) intermediate. The arene attacks the hypervalent iodine in presence of triflic acid giving the diaryliodonium salt. The scope of the reaction includes symmetric and unsymmetric salts with high yield. These electrophilic species have recently received considerable attention and are involved in a wide array of reactions.[15]



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