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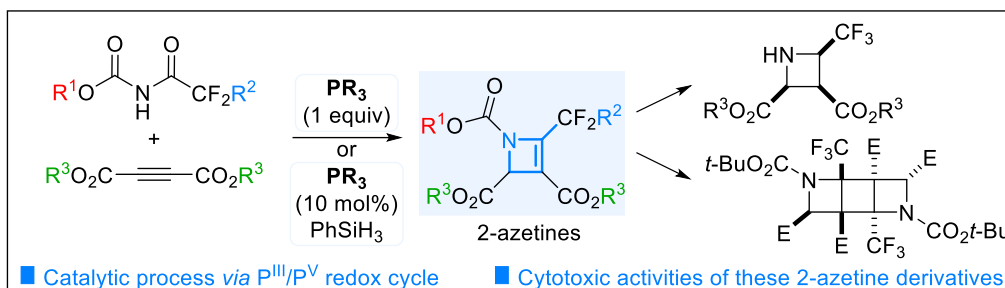


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Fluorinated 2-Azetines: Synthesis, Applications, Biological Tests and Towards the Development of a Catalytic Process

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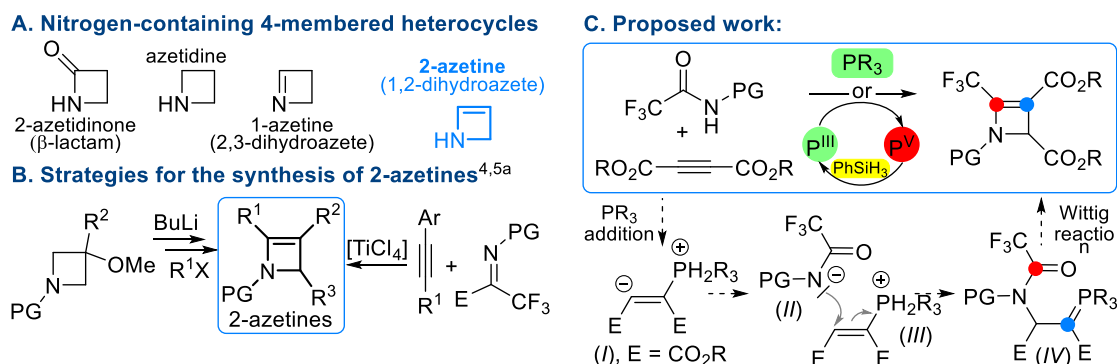
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Abstract: An efficient and straightforward phosphine-promoted tandem aza-Michael addition/intramolecular Wittig reaction has been developed for the synthesis of polyfunctionalized 2-azetines. After demonstrating that this transformation could be made catalytic in phosphine through *in situ* reduction of phosphine oxide with phenylsilane, different post-transformation steps have been demonstrated, including an original [2+2] photodimerization. Preliminary biological tests highlighted that these fluorinated 1,2-dihydroazete-2,3-dicarboxylates exhibited significant cytotoxicity against human tumor cell line.

Nitrogen-containing four-membered compounds are of huge interest in medicinal chemistry and as key intermediates for the synthesis of other heterocycles.¹ In addition to the well-known β -lactam (2-azetidinone) backbone, azetidine and its unsaturated analogues, 1-azetine and 2-azetine, have recently received increasing interest (Scheme 1A).² Because of its congested structure, the isolation of such molecules was not obvious. Indeed, the chemical stability of 2-azetines (1,2-dihydroazetes) is limited due to their potential 4π -electrocyclic ring opening to the corresponding more stable 1-aza-1,3-butadienes.³ However, when the nitrogen atom is substituted with electro-deficient protecting groups, some non-fused 2-azetines have already been synthesized. Indeed, effective strategies included elimination/substitution of 3-methoxyazetines⁴ and titanium-mediated [2+2] cycloaddition of arylalkynes with trifluoroimino pyruvates (Scheme 1B).⁵ A Cu-catalyzed [3+1] cycloaddition using iminoiodinanes and alkenyldiazoacetates^{6a} has also been developed, and subsequent studies on this reaction included an asymmetric version using imido-sulfur ylides.^{6b,c} In view of the limited number of synthetic methodologies reported for the isolation of such strained cyclic enamine derivatives,^{2,7} we designed a new phosphine-promoted (or phosphine-catalyzed) tandem formation of 2-azetines, based on a aza-Michael addition/intramolecular Wittig olefination, using dialkyl acetylenedicarboxylates (DAADs) and *N*-protected trifluoroacetamides (Scheme 1C).

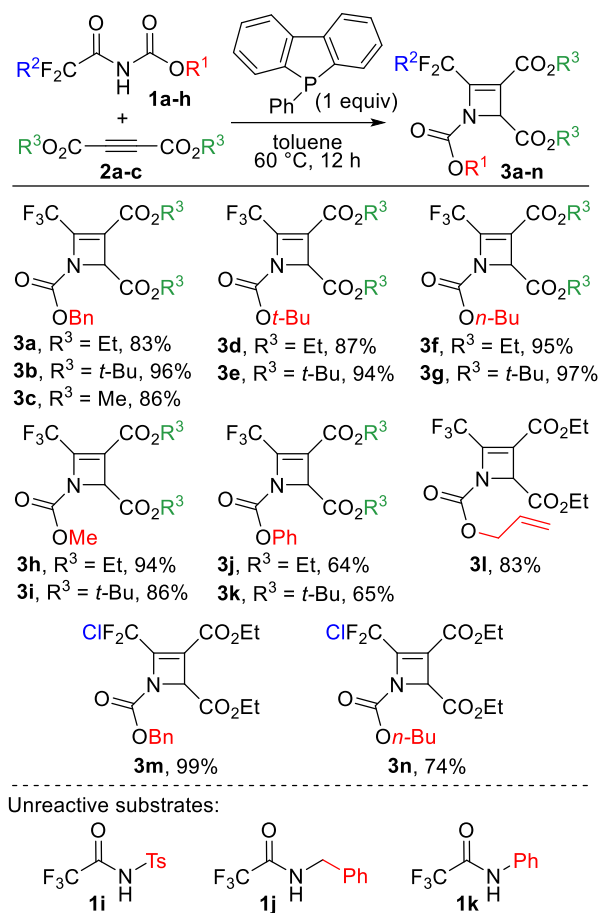
Scheme 1. Strategies for the Synthesis of 2-Azetines and Proposed Work



Related tandem processes allowed us in the past few years to access functionalized cyclobutenes, 9*H*-pyrrolo[1,2-*a*]indoles, 1,2-dihydroquinolines and tetrahydropyridines via P^{III}/P^V redox cycling.⁸ In the present case, the putative mechanism described in Scheme 1C includes the formation of the zwitterionic species (*I*), after the addition of phosphine to DAAD. After deprotonation of the nitrogen substrate and addition to the vinylphosphonium (*III*), phosphorus ylide (*IV*) is formed, without the involvement of an external base. Finally, the intramolecular Wittig reaction occurs, furnishing 2-azetine products. The key points of this work are: (1) The electron withdrawing groups directly linked to the 2-azetine backbone prevent the ring opening to the corresponding azadienes. (2) The products thus obtained can serve as a template for the synthesis of azetidines and more complex polycyclic molecules. (3) Our new methodology gives an easy access to CF₃-substituted 2-azetines, which may be of great interest considering the large number of applications of fluorinated molecules in pharmaceuticals, agrochemicals and materials.⁹ (4) Preliminary biological tests of these compounds revealed interesting cytotoxicity against acute myeloid leukaemia HL60 cell line.

We first selected benzyl (2,2,2-trifluoroacetyl)carbamate **1a** and diethyl but-2-ynedioate **2a** as model substrates, to find the best trivalent phosphine (Scheme 2).

Scheme 2. Phosphine-Promoted Tandem Transformation for the Synthesis of 2-Azetines

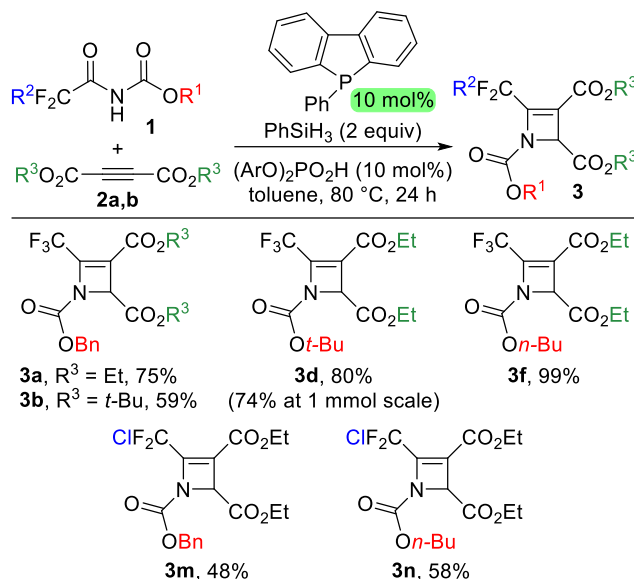


Among the different promoters tested, 5-phenyl-5*H*-benzo[*b*]phosphindole proved to be the best one, giving the desired 2-azetine **3a** in 83% yield after 12 h at 60 °C, in toluene. For comparison, a stoichiometric amount of triphenylphosphine gave **3a** in similar yield, but a reaction time of 24 h was required. These reaction conditions provided a direct route to functionalized 2-azetines with different substituents both on the DAAD substrates (R³ = Et, *t*-Bu, Me) and the carbamate derivatives (R¹ = benzyl, *tert*-butyl, *n*-butyl, methyl, phenyl and allyl). Compounds **3a-l** were thus isolated in good to excellent 64-97% yields (Scheme 2). Remarkably, these products proved to be chemically stable even during their purification on silica gel. Interestingly, the formation of polyhalogenated compounds was successful, with the synthesis of difluorochloro-compounds **3m-n** in 74-99% yields. Finally, it was attempted to extend the reactivity of the nitrogen-trifluoroacetyl precursor to *N*-tosyl, *N*-benzyl or *N*-phenyl substrates **1i-k**, unfortunately without success. Regardless of the reaction conditions used, even in refluxing toluene, these substrates do not appear reactive enough in this tandem transformation. The use of more nucleophilic phosphines, such as PBu₃ or PPhMe₂, does not yield the desired products, or leads to a complex mixture, as in the case of substrate **1i** with tributylphosphine.

A possible drawback of our methodology is the use of stoichiometric amounts of phosphine. Indeed, since the driving force of the olefination reaction is the formation of phosphine oxide, it is sometimes difficult to separate this by-product from the desired target. In order to facilitate the purification step in large-scale processes and to improve the atom economy in this reaction, we and others have developed the last decade P^{III}/P^V redox catalysis, with a strategy involving *in situ* reduction of

phosphine oxide with silane.¹⁰ To reach this goal in the present study, the catalytic protocol includes the use of 5-phenylbenzo[*b*]phosphindole as catalyst (10 mol%) and *bis*(*p*-nitrophenyl)phosphate (10 mol%) as additive, in the presence of phenylsilane (2.0 equivalents), in toluene at 80 °C (Scheme 3).

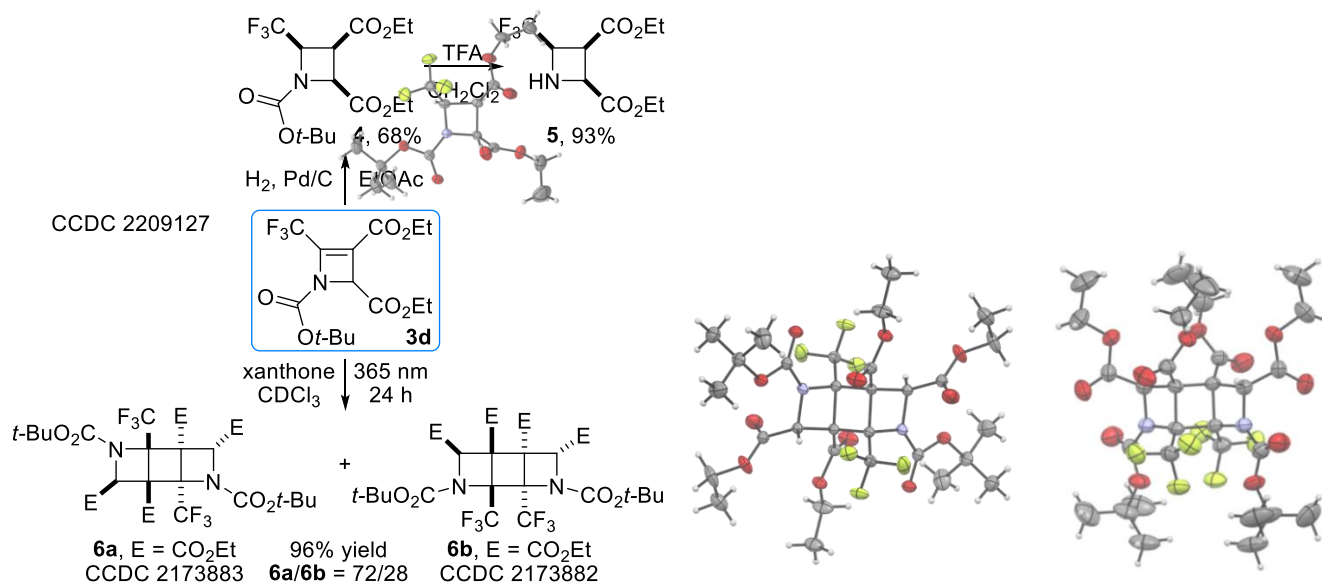
Scheme 3. Phosphine-Catalyzed Transformation via P(III)/P(V) Redox Cycling



This phosphorus catalyst presents the best compromise between the nucleophilicity of trivalent phosphine and easy reduction of the corresponding phosphine oxide. The addition of excess phenylsilane and catalytic amounts of *bis*(4-nitrophenyl)phosphate are necessary to facilitate the phosphine oxide reduction and to obtain decent yields.¹¹ Overall, the results obtained with 10 mol% of phosphine in terms of yields of 4-(trifluoromethyl)-1,2-dihydroazetes are comparable with those obtained using a stoichiometric amount of phosphine.

In view of the few methodologies developed so far for the isolation of 2-azetines, we aimed at using these compounds as “molecular Lego®” to access polysubstituted azetidines and complex polycyclic frameworks. First, hydrogenation of the double bond of compounds **3d** furnished corresponding azetidines **4** in 68% yield as a single diastereoisomer that was ascertained by X-ray crystallography. (Scheme 4).¹² Subsequently, deprotection of the nitrogen atom was achieved using trifluoroacetic acid in dichloromethane. Compound **5** was isolated in 93% yield after a basic workup.

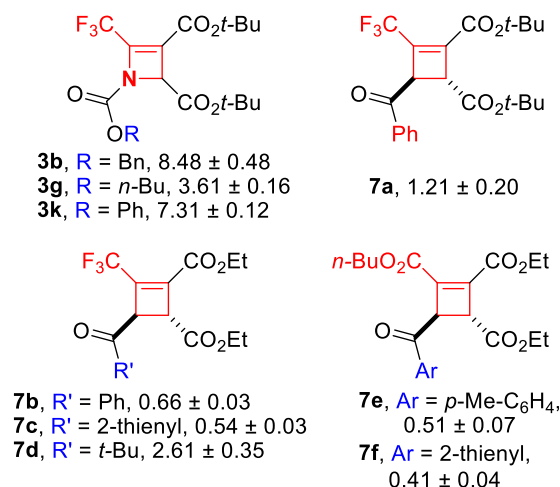
Scheme 4. Follow-up Transformations on 2-Azetines and X-ray Crystal Structure of **4 (CCDC 2209127) and the [2+2] Adducts **6a** and **6b** (CCDC 2173883 and 2173882).**



We then studied the reactivity of our new cyclic enamines through their irradiation by UV lamps.¹³ After 24 hours irradiation at 365 nm in a photochemical reactor,¹⁴ compounds **6a** and **6b** were isolated in a 72/28 ratio, both as a pure diastereoisomer (96% overall yield). Thanks to their X-ray crystal structures, **6a** was assigned as head-to-tail dimer and **6b** as a head-to-head dimer. This is a notable difference in reactivity in the [2 + 2] photocycloaddition reaction with the sole result described in the literature on dimerization of *N*-acetyl-2-azetine, where only a mixture of two diastereoisomers of head-to-head dimer was formed.¹⁵ These original 3,7- and 3,8-diazatricyclooctanes could be considered as *N*-containing analogues of ladderanes and may be of future interest in medicinal chemistry as new bioisosteres.¹⁶

Finally, the cytotoxic activities of these new 2-azetine and azetidone derivatives have been evaluated on the human acute myeloid leukaemia cell line HL60, and the most relevant results are compiled in Scheme 5. A rapid structure-activity relationship (SAR) study has provided some preliminary clues into the relative importance of some functional groups: (1) Only 2-azetines with *tert*-butyl esters groups (coming from the reaction of DAAD **2b**) exhibit a cytotoxic activity; (2) The influence of the carbamate substituent is less important on biological activity; (3) azetidines **4** and **5** are much less active (see SI for complete evaluation of cell viability and proliferation of HL60 cells). For comparison, we tested the previously synthesized carbonated analogues of 2-azetines, namely cyclobutenes **7a-f** (Scheme 5).^{8e-f} Very interestingly, submicromolar activities on HL60 human tumor cell line were found (IC₅₀ = 0.41 ± 0.04 μM) for the cyclobutene triester **7f**.

Scheme 5. Biological Evaluation of 2-Azetines and Cyclobutene Derivatives on the HL60 Human Tumor Cell Line^a



a. Cytotoxicities (IC₅₀ [μM]) of selected compounds at micromolar concentration. Data are the average ± standard error (SEM) of three independent experiments.

In summary, an efficient access to chemically stable fluorinated 2-azetines has been developed, in good yields and using mild reaction conditions. A phosphine-catalyzed version of this reaction was further demonstrated *via* P^{III}/P^V redox catalysis. This synthetic method also allows easy access to unprotected azetidines and new diazatricyclooctanes. Finally, 2-azetines and related cyclobutenes exhibit promising cytotoxic activities against HL-60 human tumor cell line. The simple access to these new complex architectural entities makes possible to pursue more advanced studies, especially in medicinal chemistry.

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