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New access to quaternary aminocyclobutanes via nucleophilic addition on cyclobutaniminium salts

Amandine Kolleth [a], Alexandre Lumbroso [a], Gamze Tanriver [b], Saron Catak [b], Sarah Sulzer-Mossé [a], Alain De Mesmaeker [a,*]

[a] Syngenta Crop Protection AG, Crop Protection Research, Research Chemistry, Schaffhauserstrasse 101, CH-4332, Switzerland
[b] Bogazici University, Department of Chemistry, Bebek, 34342 Istanbul, Turkey

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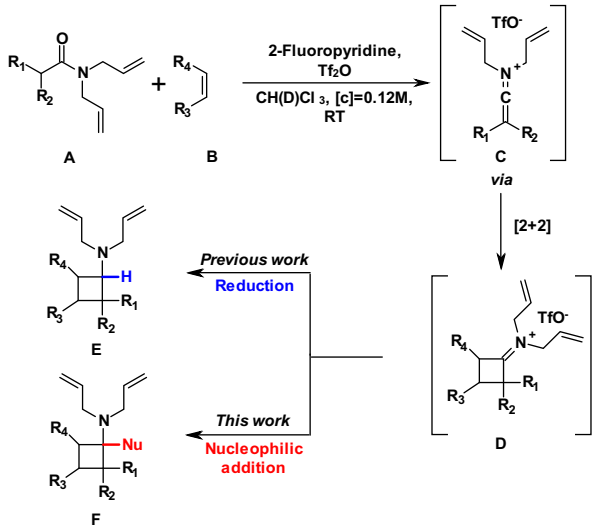
ABSTRACT

We describe the first [2+2] cycloaddition between a keteniminium salt and an alkene followed by a nucleophilic addition on the in situ generated cyclobuteniminium salts. This one-pot sequence enables the formation of quaternary centers with high level of stereoselectivity and is largely applicable to the synthesis of highly strained intermediates as well as precursor for spirohydantoïns. Moreover, DFT calculations support deuterated experiments showing that no spontaneous iminium–enamine tautomerization can exist during the [2+2] cycloaddition process.

The rigidification of the molecular backbone of a bioactive compound is an efficient way of increasing both its affinity and selectivity toward a given biological target.[1] Among the available strategies, the introduction of a cyclobutane ring[2] has been employed. In particular, aminocyclobutanes have found applications in medicinal chemistry for the design of anti-HIV compounds,[1a,3] anti-oxidants,[4] or conformationally constrained peptides.[5] In this context, the development of efficient methods to access aminocyclobutanes, which can be then easily functionalized, is highly desirable. Until recently, the synthesis of these important scaffolds relied almost exclusively on the transformation of cyclobutanones via either reductive amination[6] or Strecker reaction.[7] Therefore, there is a need for methods, which could provide access to diversely substituted and highly functionalized aminocyclobutanes.[8]

We recently developed a new method to access aminocyclobutanes[9] relying on a [2+2] cycloaddition between a keteniminium salt[10] and an alkene followed by a diastereoselective reduction step. The keteniminium salt, generated by treatment of an amide with 2-F-pyridine[11] and triflic anhydride, reacts spontaneously with an alkene to form the cyclobutaniminium salt. Reduction of this intermediate affords the corresponding aminocyclobutane in a one-pot sequence starting from the amide (Scheme 1). Moreover,



Scheme 1. Access to functionalized aminocyclobutanes.

the use of easily removable *N*-allyl moieties as protecting groups[12] largely increases the potential of this method.

Herein, we were interested in forming highly functionalized aminocyclobutanes by adding various nucleophiles (≠H) to the

* Corresponding author. Tel.: +41 628 660 268.
E-mail address: alain.de_mesmaeker@syngenta.com (A. De Mesmaeker).

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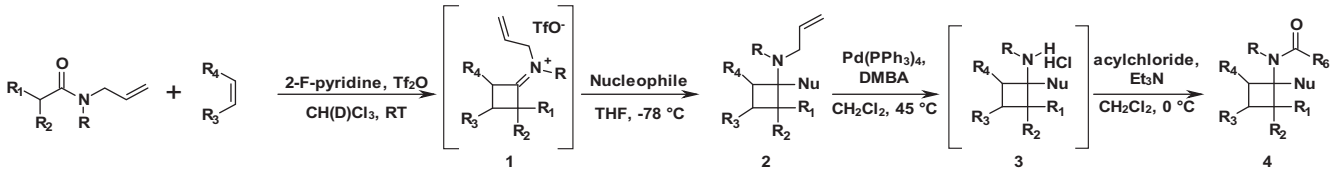
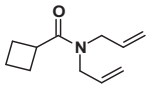
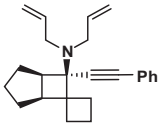
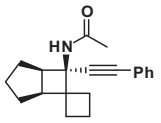
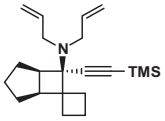
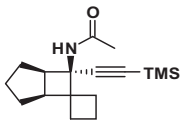
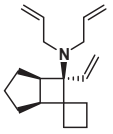
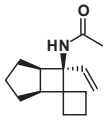
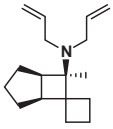
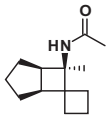
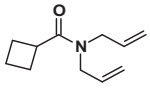
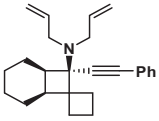
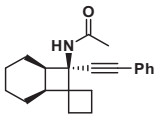
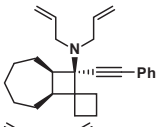
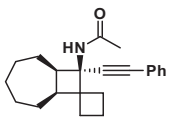
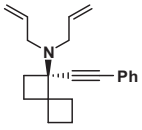
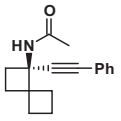
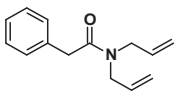
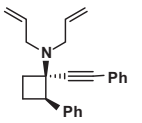
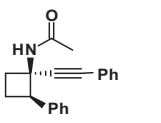
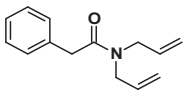
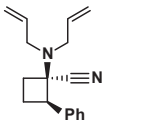
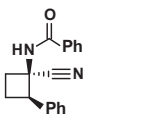
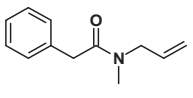
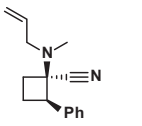
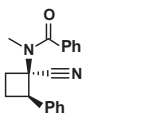
Table 1
[2+2] cycloadditions followed by nucleophilic addition, cleavage of the allyl group and amidation



Entry	Amide[a]	Alkene	Nucleophile	Product 2		Yield (%)[a]	Product 4		Yield (%)[a]
1			Ph—≡—Li		**2a**	84		**4a**	68
2			Ph—≡—MgCl·LiCl			83			
3			Ph—≡—ZnCl·LiCl			54[b]			
4			Ph—≡—$CeCl_2$			75			
5			TMS—≡—Li		**2b**	71		**4b**	77
6					**2c**	41		**4c**	83
7			MeMgBr		**2d**	42		**4d**	92
8			Ph—≡—Li		**2e**	74		**4e**	69
9					**2f**	63		**4f**	68
10					**2g**	65		**4g**	76
11			Ph—≡—$CeCl_2$		**2h**	61 (30)[c]		**4h**	89
12			TMS—≡—N		**2i**[d]	50		**4i**	67[e]
13			TMS—≡—N		**2j**[d]	64		**4j**	47

[a] Isolated yield after purification by flash chromatography on silica gel.
[b] Nucleophilic addition was carried out at RT.
[c] Lithium phenylacetylide was used.
[d] The cyanation was carried out directly by adding TMSCN (3 equiv) and Bu_4NCN (0.1 equiv) to the reaction mixture from the previous step.
[e] Peptide coupling was performed instead of amidation with acylchloride: $PhCO_2H$ (1 equiv), DIPEA (2.5 equiv), HATU (1 equiv), DMF, RT, 12 h.