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Recent developments in the synthesis and reactivity of methylene- and alkylidenecyclopropane derivatives

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Abbreviations: acac, acetylacetonate; Ad, adamantyl; AIBN, 2,2′-azobisisobutyronitrile; Ar, aryl; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bppf, 9,9-bis[4-(pyrenyl)phenyl]-9*H*-fluorene; Bs, *p*-bromobenzenesulfonyl (brosyl); Bz, benzoyl; Cod, cyclooctadiene; Cy, cyclohexyl; Dba, dibenzylideneacetone; DBU, 1,8-diazabicyclo[5.4.0]undecen-7-ene; DCE, 1,2-dichloroethane; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; de, diastereomeric excess; DIBAL, diisobutylaluminum hydride; DMAc, *N*,*N*-dimethylacetamide; DMF, dimethylformamide; DMP, Dess–Martin periodane; DMSO, dimethylsulfoxide; DOSP, *N*-(dodecylbenzenesulfonyl); E, electrophile; ee, enantiomeric excess; EWG, electron-withdrawing; Fu, furyl; HMDS, hexamethyldisilazide; Hept, heptyl; Hex, hexyl; IBAZ, isobutyl 2-oxoazetidin-4-carboxylate; L, ligand; LDA, lithium diisopropylamide; MAD, methyl aluminium bis(2,4,6-tri-*tert*-butyl-4-methylphenoxide); MEM, 2-methoxyethoxymethyl; Mes, mesyl; MOM, methoxymethyl; MS, molecular sieves; Naph, naphthyl; NBS, *N*-bromosuccinimide; NMO, *N*-methylmorpholine *N*-oxide; Ns, nosyl; Oct, octyl; Pent, pentyl; PFL, *Pseudomonas fluorescens*; PHANEPHOS, 4,12-bis(diphenylphosphino)-[2.2]-paracyclophane; Phth, phthaloyl; Pin, pinacol; Piv, pivalate; rt, room temperature; TBAF, tetra-*n*-butylammonium fluoride; TBS, *tert*-butyldimethylsilyl; *t*-Bu-XPhos, 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl; TCE, 2,2,2-trichloroethanol; TEA, triethylamine; Tf, trifluoromethanesulfonyl; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMEDA, tetramethylethylenediamine; TMS, trimethylsilyl; Tol, tolyl; TPAP, tetrapropylammonium perruthenate; Ts, 4-toluenesulfonyl (tosyl); Xantphos, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene.

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1. Introduction

The importance of strained carbocycles has long been recognised in organic chemistry.[1] In particular, organic chemists have always been fascinated by the cyclopropane subunit,[2] which has played and continues to play a prominent role in organic chemistry. Its strained structure, interesting bonding characteristics, and value as an internal mechanistic probe have attracted the attention of the physical organic community. Due to the limited degrees of freedom in the system, these conformationally constrained molecules have very pronounced steric, stereoelectronic and directing effects, which make them versatile probes for the study of regio-, diastereo- and enantioselectivity.[3] Furthermore, a diverse reactivity pattern resulting from the significant strain energy accounts for the use of small carbocycles as convenient models for the investigation of organic and organometallic reaction mechanisms.[4] The growing interest in small carbocycles is also closely related to the fields of medicinal and biological chemistry.[5] Indeed, while the cyclopropane ring is a highly strained entity, it is nonetheless found in a wide variety of naturally occurring compounds including terpenes, pheromones, fatty acid metabolites and unusual amino acids.[6] Cyclopropane subunits also occur in many natural products of primary and secondary metabolism. Indeed, the prevalence of cyclopropane-containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, such as among many others G1499-2, amphimic acids, and 9-hydroxymethylcyclopropylidene-methylenyladenine,[7] has inspired chemists to find novel and diverse approaches to their synthesis.[8] Naturally occurring and synthetic cyclopropanes bearing simple or complex functionalities are endowed with a large spectrum of biological properties, including enzyme inhibition, and insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumour and antiviral activities.[9] It must be noted that methylenecyclopropane is the smallest carbocycle with an *exo*-methylene moiety.[10] A number of methylenecyclopropanes have been recently developed by the group of Zemlicka as unusual analogues of nucleosides and established as powerful antiviral agents against a broad range of viruses.[11] Among the class of cyclopropanes, methylene- and alkylidenecyclopropane derivatives have been well documented as useful synthetic intermediates in organic chemistry over the past few decades. Arguably, the chemistry of these compounds is the most rapidly developing among all small-ring compounds. Indeed, alkylidenecyclopropanes and methylenecyclopropanes are highly interesting compounds. Surprisingly, in spite of their highly strained structure (40 kcal mol^{-1}), they usually exist as stable compounds at room temperature, allowing their use in many synthetic applications with an otherwise unattainable chemical reactivity. Because of this strained nature, associated with a large structural differentiation available, methylene- and alkylidenecyclopropanes show various reactivities and have long been widely used in organic synthesis for their enormous potential,[12] in particular to achieve heterocycles.[13] In this context, numerous efficient and straightforward syntheses of different types of methylene- and alkylidenecyclopropanes have appeared in the literature.[12b,14] The goal of the present review is to cover the recent advances in the synthesis and reactivity of methylene- and alkylidenecyclopropane derivatives, focussing on those published in the last four years. This area was previously reviewed by Guo and Yu in 2011, covering the literature until the beginning of 2010.[12b] This review is subdivided into two parts, dealing successively with the synthesis and the reactivity of methylene- and alkylidenecyclopropanes. The first part is subdivided into two sections, according to the different methods employed to prepare these compounds, such as those based on the formation of the cyclopropane ring, and those based on the use of preformed cyclopropane ring. The second part of the review is subdivided into five sections, according to the different types of reactions, such as transition metal-catalysed reactions, Lewis and protic acid-catalysed reactions, thermal cycloadditions, miscellaneous non-catalysed reactions and radical reactions.

2. Synthesis of methylene- and alkylidenecyclopropanes

Since the methylenecyclopropane moiety is found in many biologically active natural substances, the synthesis of methylene- and alkylidenecyclopropanes remains a considerable challenge. In addition, their attractive feature is their surprising stability, accompanied by a high level of strain, conferring on them an otherwise unattainable chemical reactivity. The growing interest in the chemistry of these compounds has in its turn stimulated the development of alternative approaches to their skeleton, aimed at selectively introducing structural and chemical diversification. The two principal methods to synthesise these important compounds are based on the formation of the cyclopropane ring, and the use of preformed cyclopropanes. During the last several years, chemists have developed various novel reactions leading to methylene- and alkylidenecyclopropanes. The last methodologies allowing a more direct access to these structures are collected in this section.

2.1. Formation of the cyclopropane ring

The carbene (or carbenoid) addition to unsaturated compounds is undoubtedly the most useful and straightforward preparative method for alkylidenecyclopropane derivatives. It is one of the first general methods thoroughly applied for the assembly of the alkylidenecyclopropane moiety, with reports appearing since the early 1960s. There are two variants for these addition reactions, which are the addition of alkylidenecarbenes to olefins, and the addition of generated carbenes to allenes, as summarised in Scheme 1.

The first variant for preparative method for alkylidenecyclopropane derivatives consists in the addition of alkylidenecarbenes to olefins, and has been investigated for more than 40 years. It must be noted that, however, most of the work reported on this subject has been focused on mechanistic and theoretical aspects with the