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Intramolecular Baylis-Hillman Reaction

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Abstract
The Baylis–Hillman reaction is a novel atom economic, carbon-carbon bond forming three component reaction between activated alkene and carbon electrophile under catalytic influence of a catalyst/catalytic system. This review highlights developments of the intramolecular version of Baylis-Hillman adduct in the last three decades.

Keywords: Carbon-carbon bond forming reaction, intramolecular B-H reaction, biologically important molecules, 1,4-Diazabicyclo (2.2.2) octane

1. Introduction

The recent developments in organic chemistry mandate the nonstop convenient methodologies for carbon-carbon bonds formation and functional group transformation strategies with simple processes. The Baylis-Hillman reaction [1-3] is tertiary amine catalytic three component, atom economical carbon-carbon bond forming reaction. Baylis-Hillman reaction is a coupling reaction of α-position of activated alkenes with electrophiles under the influence of a tertiary amine catalyst, providing fascinating class of densely functionalized molecules (Fig. 1). The Baylis-Hillman reaction [4, 5] invention by American chemists A. B. Baylis and M. E. D. Hillman in the year 1973.

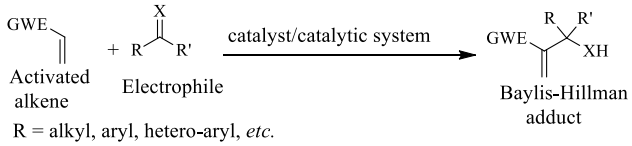
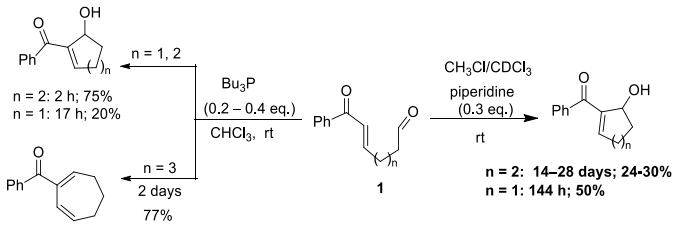


Fig. 1 General equation

Intramolecular Baylis-Hillman reaction

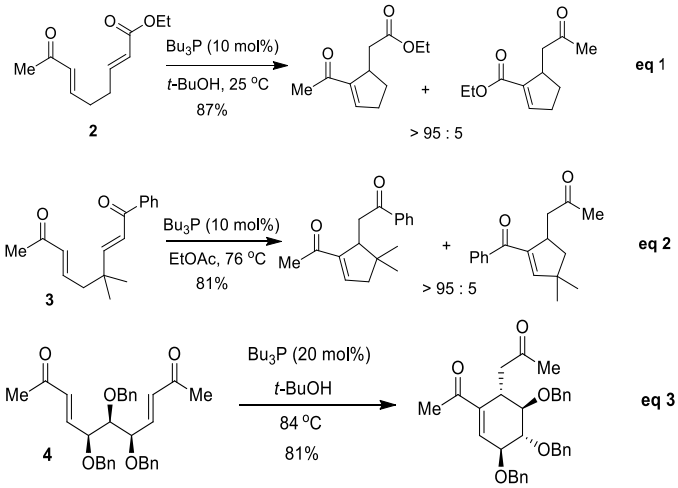
If the substrates contain both the activated alkene and electrophile components in appropriate position, there is possibility for performing intramolecular version of Baylis-Hillman reaction providing cyclic adducts. During the last several years this reaction has developed with respect to all the three essential compounds i.e. (1) Electrophiles, (2) Activated alkenes and (3) Catalysts or catalytic systems. Although there have been great advances in the case of all the three essential components, it is exciting to note that the intramolecular version remains at beginning. However, in this aspect has received more consideration from the synthetic chemists and significant progress has been reached. The interesting developments in this way are presented in this paper.

Murphy and co-workers [6, 8] have reported an intramolecular version of Baylis–Hillman reaction of enolaldehydes (1) in the presence of secondary amine (piperidine) or Bu_3P to offer the corresponding Baylis–Hillman adducts or eliminated cycloheptadiene (Scheme 1).



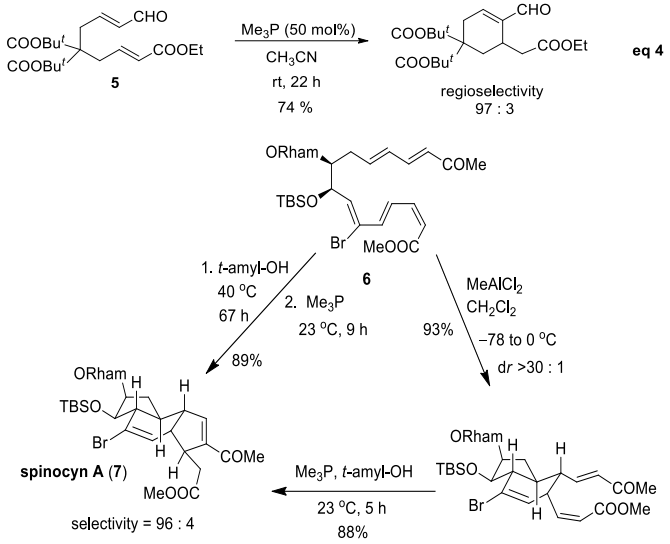
Scheme 1

Krische and co-workers [9] published an interesting Bu_3P catalyzed cycloisomerization of bisenones (2 & 3). They have examined the effect of electronic (eq 1) and steric factors (eq 2) on cyclization. They have also further studied this methodology for the diastereoselective intramolecular Baylis–Hillman reaction of chiral bisenone (4) derived from xylose (eq 3) [9].



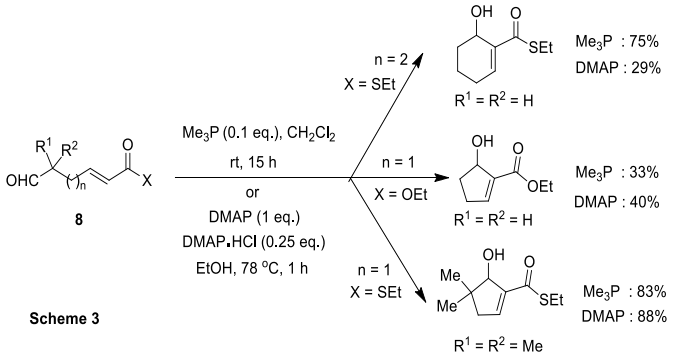
Roush and co-workers [10] reported an intramolecular

Baylis–Hillman reaction of diactivated dienes (5) for synthesis of functionalized cycloalkene derivatives (eq 4). Next they have applied this methodology for the transformation of the molecule 6 into tricyclic nucleus of spinosyn A [11] (7) (Scheme 2).



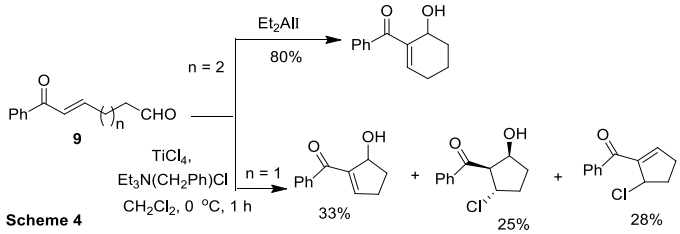
Scheme 2

Keck and Welch[12] stated an intramolecular version of the Baylis–Hillman reaction of α,β-unsaturated esters/thioesters (8) containing enolizable aldehyde group under various conditions (Scheme 3).



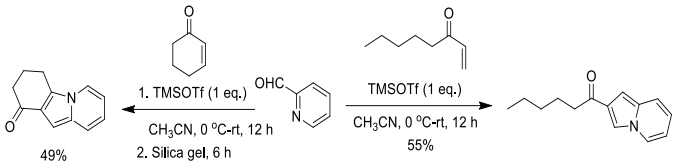
Scheme 3

Oshima and co-workers [13] described Lewis acid mediated intramolecular Michael and aldol cyclization of formyl α,β-enones (9). Thus, the reaction of 9 with Et_2AlI provided the Baylis–Hillman adduct, where as the similar reaction with titanium tetrachlo-ride/triethylbenzylammonium chloride provided the Baylis–Hillman compound along with intramolecular chloro aldol product and dehydration product (Scheme 4).



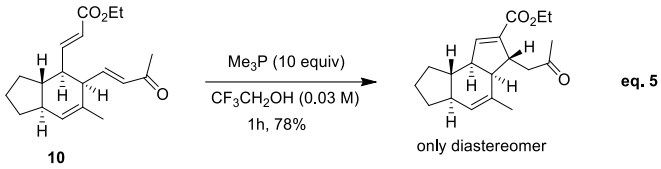
Scheme 4

Basavaiah and Rao[14] reported an electrophile induced intramolecular Baylis–Hillman reaction between activated alkenes and pyridine-2-carboxldehyde under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), leading to a novel synthesis of indolizine derivatives in one-pot operation (Scheme 5).

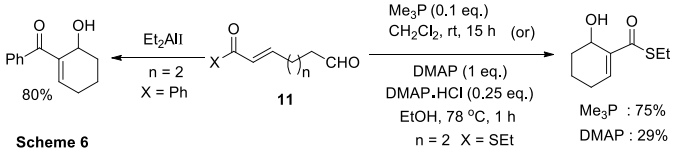


Scheme 5

Methot and Roush[15] have reported an interesting intramolecular Baylis-Hillman reaction of 10 under the influence of Me_3P (eq. 5).

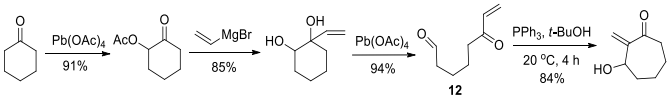


Intramolecular Baylis–Hillman reaction ofα,β-unsaturated systems (11) containing enolizable aldehyde group, has been recently reported by Keck & Welch [16] (using Me_3P or DMAP, DMAP.HCl) and later on by Oshima and co-workers[17] (using Et_2AlI) (Scheme 6).



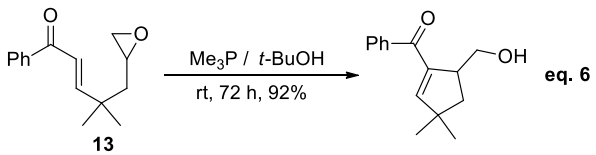
Scheme 6

Very recently, Koo *et al.* [18] have reported an efficient method for the preparation of diverse formyl unsaturated carbonyl compounds (12) and successfully employed them in intramolecular Baylis-Hillman reactions (Scheme 7).

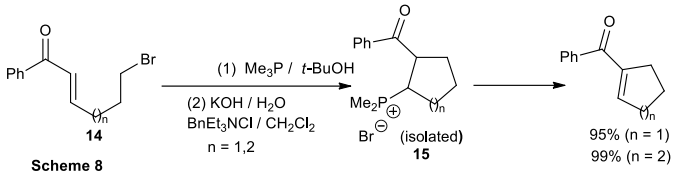


Scheme 7

Kraft and Wright [19] reported trialkyl phosphine mediated Baylis-Hillman ring closing reaction of enone-epoxide system (13) to obtain the cyclic adducts in good yields (eq. 6).

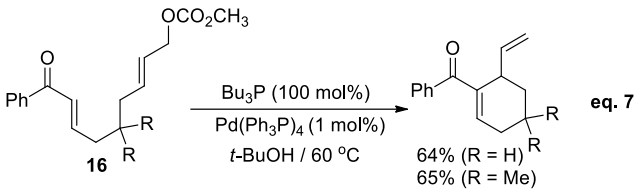


Krafft and coworkers [20] published an organo-base mediated intramolecular Baylis-Hillman cyclization of enones (14) to provide the corresponding cyclic molecules (five and six-membered rings) in excellent yields. With a view to understand the mechanism they have also isolated and characterized ketophosphinium salt (15) which is the key intermediate (Scheme 8) [21].



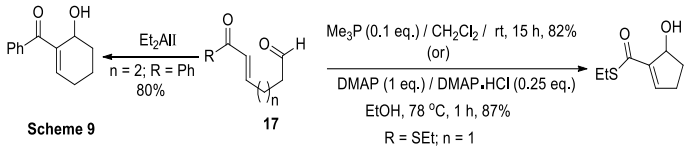
Scheme 8

An intramolecualr ring closing reaction of the enone-carbonates (16) under the 0069nfluence of Bu [3] P in the presence of catalytic amount of $Pd(Ph_3P)_4$ to provide a convenient method for synthesis of functionalized cycloalkenes was described by Krische and coworkers [22] (eq. 7).



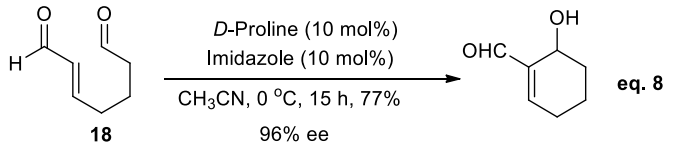
eq. 7

Oshima [23] reported an interesting intramolecular Baylis-Hillman reaction of substrates (17) having both the activated alkene moiety and electrophile component leading to the synthesis of cyclopentene (R = SEt; n = 1) and cyclohexene (R = Ph; n = 2) derivatives (Scheme 9).



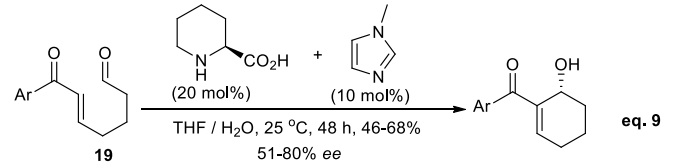
Scheme 9

For the first time, Hong and coworkers [24] demonstrated an efficient proline catalyzed enanatioselective intramolecular Baylis-Hillman reaction of enone-aldehyde system (18) under the influence of imidazole (eq. 8).



eq. 8

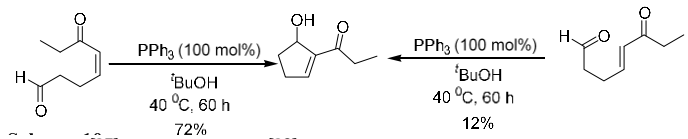
Miller and coworkers [25] reported, the application of (*S*)-2-pipecolinic acid for promoting asymmetric intramolecular Baylis-Hillman reaction of enone-aldehyde system (19) in the presence of *N*-methylimidazole to provide the resulting adduct in good enantioselectivities (eq. 9).



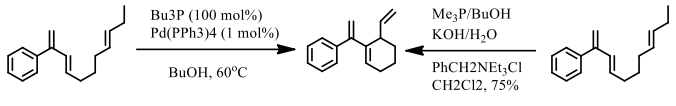
eq. 9

Ar = Phenyl, 2-methylphenyl, 4-chlorophenyl, 4-bromophenyl, thiophen-2-yl

Shi and coworkers [26] reported an interesting intramolecular Baylis-Hillman reaction of enone-aldehyde under the influence of PPh_3. They have observed the role of stereochemistry of double bond in enone-aldehyde system. Thus, the substrate with (*Z*)- stereochemistry afforded much higher yield than the corresponding substrate with (*E*)stereochemistry (Scheme 10).

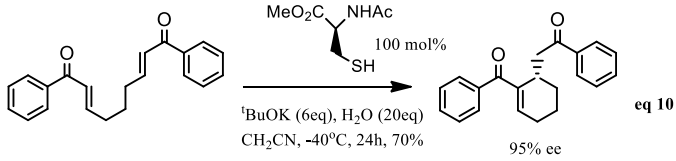


Krishe [27] and Krafft [28] have independently reported an interesting intramolecualr Baylis-Hillman reaction of the enone-allyl carbonates and enone-allyl alcohol respectively as substrates to provide convenient methodologies for synthesis of functionalized cycloalkenes (Scheme 11).



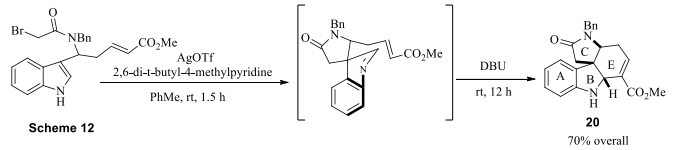
Scheme 11

Aroyan and Miller [29] have examined the asymmetric intramolecular Baylis-Hillman reaction of bisenone in the presence of cysteine derivative which provided the corresponding functionalized cyclohexene derivatives in good yields with high enantioselectives (eq. 10).



eq 10

Andrade and Sirasani [30] have published a methodology by a novel sequential one-pot alkylation and intramolecular Baylis-Hillman reaction for synthesis of ABCE tetracyclic framework (20) of *Strychnos* alkaloids (Scheme 12)

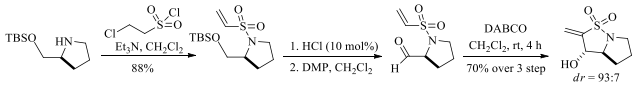


Scheme 12

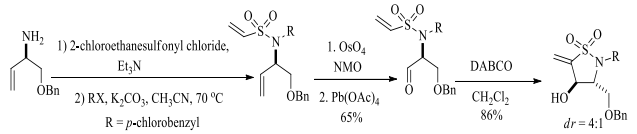
20

70% overall

Hanson and coworkers [31, 32] have reported intramolecular Baylis-Hillman reaction as the key step to generate sultams *via* a strategy involving functional group pairing between vinyl sulfonamide and suitably protected amino alcohol/aldehyde following the reaction sequences (Schemes 13 & 14).

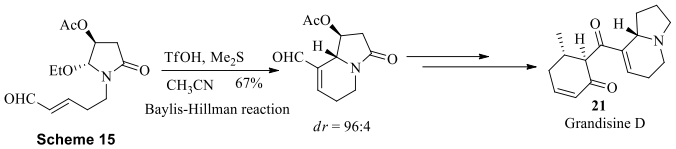


Scheme 13



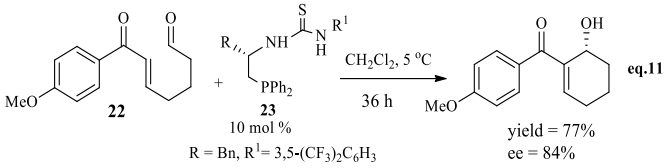
Scheme 14

Total synthesis of grandisine D (21) was reported by Tamura and coworkers [33] using Bronsted acid mediated intramolecular Baylis-Hillman reaction as the key step (Scheme 15).

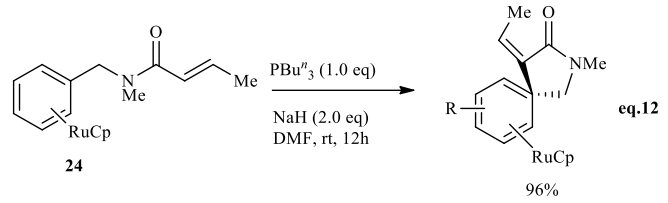


Scheme 15

Wu co-workers [34] demonstrated an interesting intramolecular asymmetric Baylis-Hillman ring closing reaction of enone-aldehyde substrate (22) using chiral amino acid derived phosinothiourea as a catalyst (23) (eq. 11).



Pigge and co-workers[35] reported an interesting organometallic intramolecular Baylis-Hillman reaction. In this reaction ruthenium-arene complex (24) is employed as an electrophile to provide the resulting spiro adduct with 100% diastereoselectivity (eq. 12).



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