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Advances in the Baylis–Hillman reaction-assisted synthesis of cyclic frameworks☆

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This article is dedicated to Professor D. Basavaiah for his seminal contributions toward development of this reaction

Keywords: Baylis–Hillman reaction; Cyclic compounds; Heterocycles; Nucleophilic substitution

Contents

Abbreviations: Ac, acetyl; AIBN, 2,20-azobisisobutyronitrile; Aq, aqueous; Ar, aryl; 9BBN, 9-borabicyclo[3.3.1]nonane; BINAP, 2,20-bis(diphenylphosphanyl)-1,10-binaphthyl; $BF_3{\cdot}Et_2O$, boron trifluoride etherate; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu, butyl; *c*, *cyclo*; CAN, ceric(IV) ammonium nitrate; cat., catalyst; Cp, cyclopentadienyl; DBU, 1,8-dazabicyclo[5.4.0]undec-7-ene; DCE, 1,2-dichloroethane; DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; de, diastereomeric excess; DIBAL-H, diisobutylaluminum hydride; DIEA, diisopropylethylamine; DMAD, dimethyl acetylenedicarboxylate; DMAP, 4-dimethyl aminopyridine; DME, 1,2-dimethoxyethane; DMF, dimethylformamide; DMSO, dimethylsulfoxide; dppp, 1,3-bis(diphenylphosphino)propane; dr, diastereomeric ratio; DYKAT, dynamic asymmetric kinetic transformation; ee, enantiomeric excess; Et, ethyl; $EtPh_2P$, ethyldiphenylphosphine; EWG, electron-withdrawing group; Hex, hexyl; HFIP, hexafluoro-2-propanol; HFIPA, 1,1,1,3,3,3-hexafluoroisopropyl acrylate; HMDS, bis(trimethylsilyl)amide; HMP, hexamethyl phosphoramide; 3-HQD, 3-hydroxyquinuclidine; HMTA, hexamethylenetetramine; IBX, *o*-iodoxybenzoic acid; β-ICD, β-isocupreidine; LDA, lithium diisopropylamide; *m*-CPBA, *m*-chloroperoxybenzoic acid; Me, methyl; Ms, mesyl; MOM, methoxymethyl; MS, molecular sieves; MVK, methyl vinyl ketone; MW, microwave; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NMO, *N*-methyl morpholine-*N*-oxide; Ns, *p*-nitrobenzenesulfonyl; Nu, Nucleophile; $(o\text{-Tol})_3P$, tri-*ortho*-tolyl-phosphine; PCC, pyridinium chlorochromate; PEG, polyethylene glycol; Pent, pentyl; Ph, phenyl; PMB, *p*-methoxybenzoyl; PMDETA, *N*,*N*,*N*′,*N*′,*N*-pentamethyldiethylinetriamine; Mont., Montmorillonite; PPA, polyphosphoric acid; Pr, propyl; RCM, ring-closing metathesis; RDS, rate-determining step; rt, room temperature; SES, 2-trimethylsilylethylsulfonyl; *t*-Bu, tertiarybutyl; TBAF, tetrabutylammoniumfluoride; TBS or TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TBHP, tetrabutylhydroperoxide; TFA, trifluoroacetic acid; TFAA, trifluoroacetic anhydride; TFE, trifluoroethanol; TfOH, triflic acid or trifluoromethanesulfonic acid; THBP, 2,4,5-trihydroxybutyrophenone; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulfonate; Tol, toluene; TPAP, tetrapropylammonium perruthenate; Ts, tosyl or 4-toluenesulfonyl; TsOH, *p*-toluenesulfonic acid; TTMSS, tris(trimethylsilyl)silane; us, ultrasound.

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1. Introduction

Acquiring the capability to access structurally complex and diverse molecules through simple starting substrates has been one of the underlying principles of chemical research. These diverse compounds are desired in order to serve mankind in a variety of ways. They might find use in pharmaceutical, agriculture, dyes, materials, electronics, and so forth. With the objective of generating an enormously complex skeletal diversity, chemists are always on the lookout for efficient complexity-generating reactions, also referred to as tandem reactions.[1] These reactions may directly lead to a complex product from small and simple building blocks in a single operation or may lead to a product that is multifunctional and becomes a substrate for another complexity-generating reaction. Some of the examples of this class of reactions include the Ugi reaction, Passerini reaction, Diels–Alder reaction, ring-closing metathesis, and Baylis–Hillman reaction.

The Baylis–Hillman reaction, a carbon–carbon bond-forming reaction, which basically involves a reaction between an aldehyde (**1**) and an activated alkene (**2**) in the presence of a tertiary base, affords a highly functionalized product (**3**) (Fig. 1). As described by Basavaiah et al. in their recent review, it is a three-step reaction involving successive Michael, aldol, and elimination reactions in one pot.[2] The cheap and easy availability of starting materials, ease of performance (since it can be executed in water), atom economy, formation of chemospecific functional groups in the product, provision of an avenue for the introduction of asymmetry, and suitability for simulation on the solid phase as a prelude for combinatorial synthesis represent some of the reasons, which have led to an exponential increase in the synthetic utility of this reaction.

The reaction came into existence in 1968, when H. Morita disclosed that the reaction of an aldehyde with an activated alkene in the presence of tricyclohexylphosphine (PCy_3) affords a densely functionalized product (Fig. 2). Subsequently, he published a series of patents detailing the utility of his strategy.[3] This reaction, however, earned its name from Baylis and Hillman, who reported that the reaction of aldehydes with activated alkenes including esters, amides, nitriles, and ketones in the presence of tertiary bicyclic amines furnished multifunctional products (Fig. 2).[4] The synthetic appreciation of this reaction in organic chemistry was at a low ebb during the initial phase. When the utility of the Baylis–Hillman reaction for the synthesis of integerrinecic acid and mikanecic acid was, however, demonstrated by Drewes and Emslie[5] in 1982 and Hoffmann and Rabe[6] in 1983, respectively, various chemists became interested in it and started investigating its utility. This led to the publication of the first review in 1988 by Drewes and Roos.[7] Since then, investigations into different aspects of the Baylis–Hillman

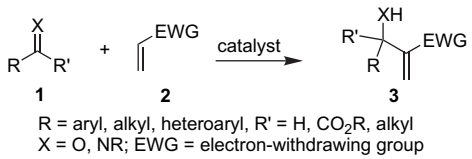

Figure 1. General representation of the Baylis–Hillman reaction.

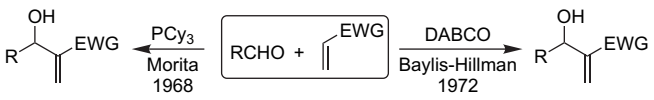

Figure 2. Reactions embodied in patents by Morita and Baylis–Hillman.