Asymmetric Synthesis of Baylis-Hillman Reaction

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Abstract— Asymmetric synthesis of 3-substituted 3-hydroxyoxindoles which could serve as valuable synthetic building blocks. Their described the first example of diastereo- and enantio-selective aza-MBH-type reaction was accomplished by the asymmetric synthesis of *β*-nitro-*γ*-enamines *via* a (1R,2R)-diaminocyclohexane thiourea derivative mediated tandem Michael addition and aza-Henry reaction Construction of the first chemo- and *a* -regioselective asymmetric Michael addition of *γ,γ*-disubstituted *a,β*-unsaturated aldehydes to nitroolefins has been presented in excellent diastereo- and enantioselectivities (dr up to >99:1, 93-96% ee) via dienamine catalys. This Focus Review provides a summary of recent approaches to catalytic asymmetric synthesis of Baylis-Hillman derivatives.

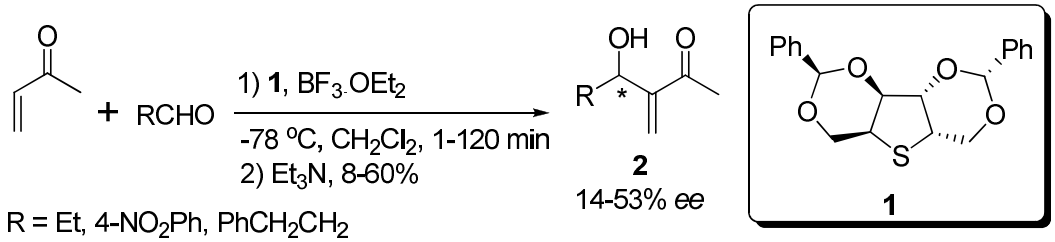
Keywords— Baylis-Hillman adducts, aza-MBH, Henry reaction, nitroolefins, dienamine catalys, *β*-nitro-*γ*-enamines.

INTRODUCTION

Several approaches to the synthesis of different types of asymmetric synthesis of Baylis-Hillman derivatives have been reported. However, a comprehensive review covering stereo selective approaches to asymmetric bicycle compounds. Therefore, we have summarized herein the recent stereo selective approaches, particularly catalytic asymmetric synthesis of Baylis-Hillman reaction. Fictionalization of electron deficient alkenes at the α-position, normally under amine or phosphine catalyzed conditions, popularly known as the Morita-Baylis-Hillman (MBH) reaction, is an efficient methodology for the synthesis of multi-functional molecules. Stereo chemically inflexible heterocyclic compounds are the building blocks of novel non-natural peptides and proteins with improved and unusual biological properties such as helix-inducing potential, enhanced resistance against chemical and enzymatic hydrolysis, and so forth.[1-5]

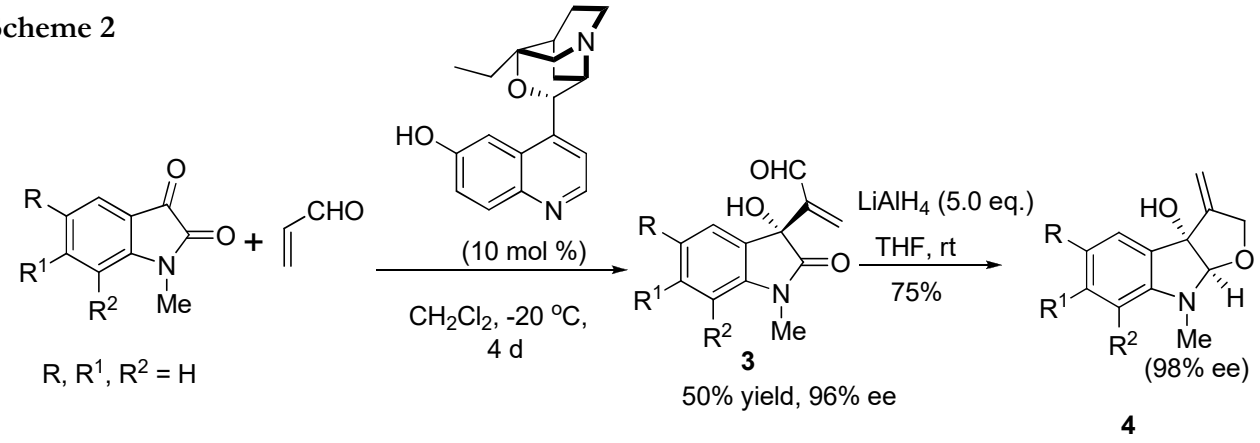
Goodman and coworkers[6] have reported tetrahydrothiophene-BF_3.OEt_2 mediated Baylis-Hillman reaction of MVK with aldehyde. They used enantiopure sulfide (**1**), which provided the desired Baylis-Hillman adducts (**2**) with 53 % enantiomeric excess as shown in Scheme 1.

Scheme 1



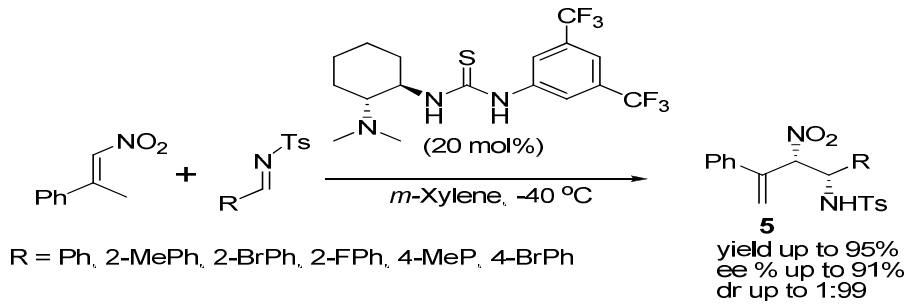
Zhou and co-worker[7] have developed a highly enantioselective Morita-Baylis-Hillman (MBH) reaction of isatins and acrolein to provide enantiomerically enriched 3-substituted 3-hydroxyoxindoles, which could serve as valuable synthetic building blocks. This is also the first time that a ketone has been used as the electrophile and acrolein as the nucleophile in a highly enantioselective catalytic asymmetric MBH reaction as shown in Scheme 2.

Scheme 2



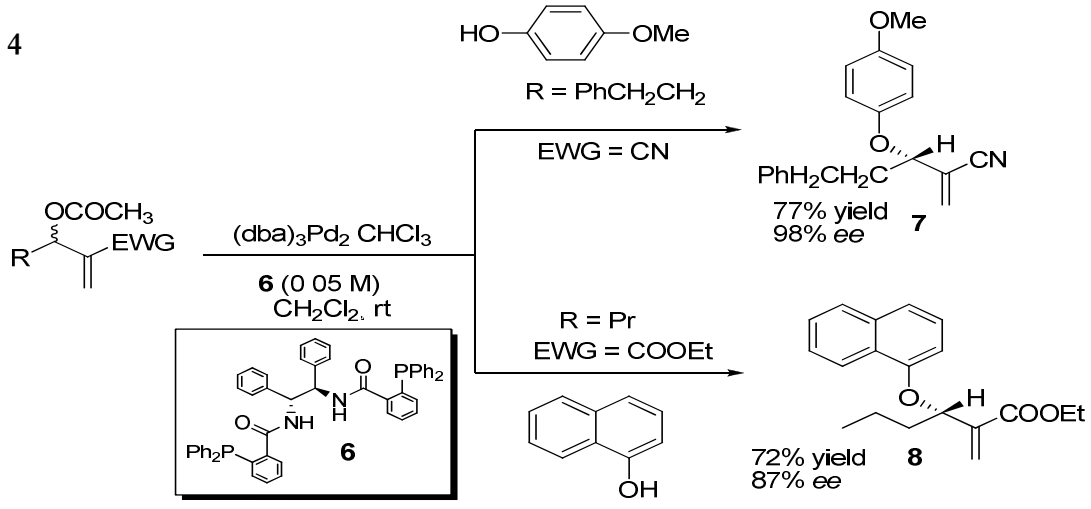
Xu and coworkers[8] have described the first example of diastereo- and enantio-selective aza-MBH-type reaction was accomplished by the asymmetric synthesis of *β*-nitro-*γ*-enamines *via* a (1R,2R)-diaminocyclohexane thiourea derivative mediated tandem Michael addition and aza-Henry reaction (**5**) as shown in Scheme 3.

Scheme 3



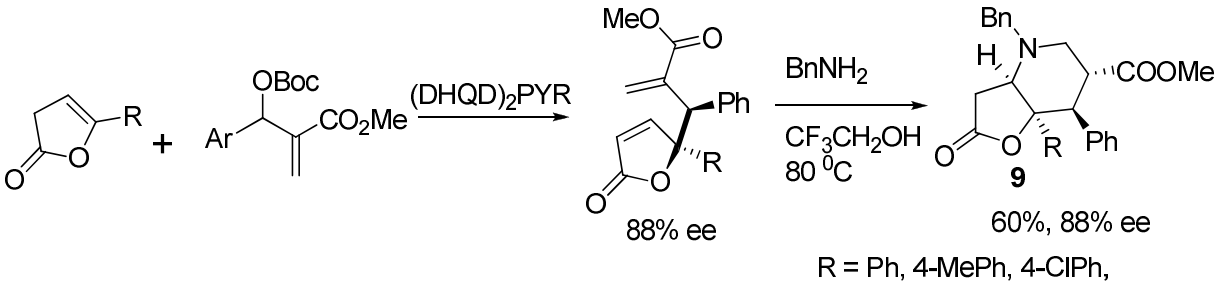
Several efforts have been made in this direction using various chiral-activated alkenes such as chiral acrylates and chiral aldehydes as electrophiles and asymmetric catalysts. Trost *et al*[9] have reported elegant de-racemization of Baylis-Hillman adducts following an alternative approach with $(dba)_2Pd_2.CHCl_3$ and enantiopure ligands such as **6**. One representative example is described in Scheme 4.

Scheme 4



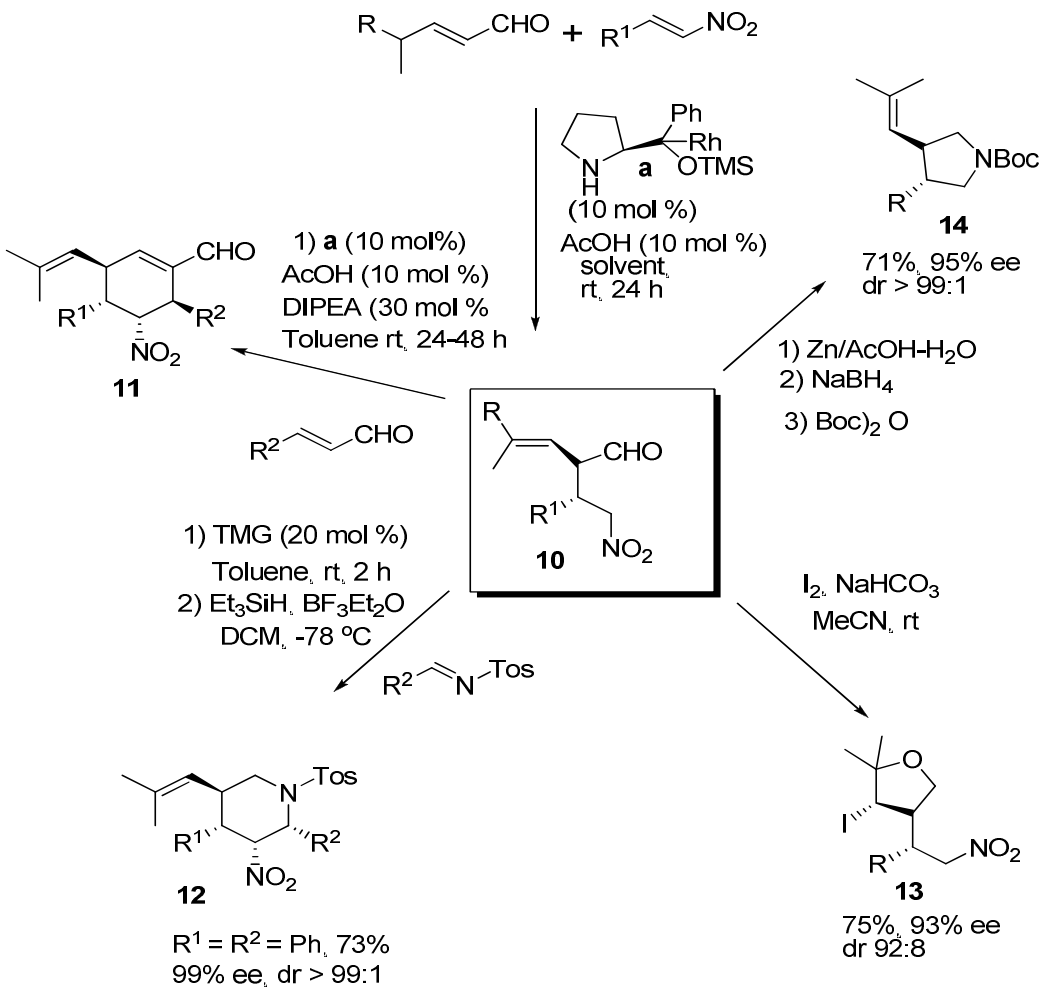
chen and coworkers[10] have developed the direct asymmetric allylic alkylation of *γ,γ*-butenolides with MBH carbonates to access *γ,γ*-disubstituted butenolides containing adjacent quaternary and tertiary chiral centers has been presented in excellent stereoselectivities (86-96% *ee*, dr >95:5) and moderate to good yield (50-83%). Their synthetic utility has been well demonstrated by the facile construction of bicyclic lactones bearing 4-5 stereogenic centers as shown in Scheme 5.

Scheme 5



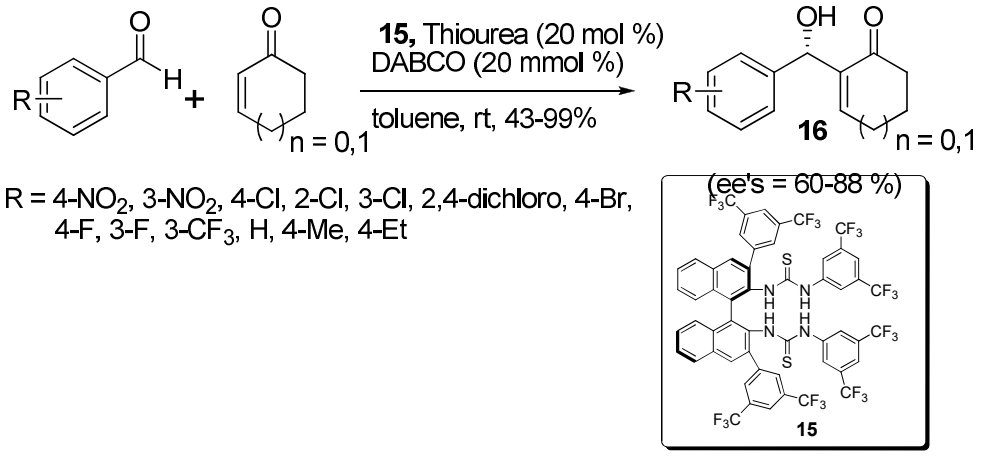
Chen and co-workers[11] have reported the first chemo- and *a* -regioselective asymmetric Michael addition of *γ,γ*-disubstituted *a,β*-unsaturated aldehydes to nitroolefins has been presented in excellent diastereo- and enantioselectivities (dr up to >99:1, 93-96% ee) via dienamine catalysis. The Michael adducts have been efficiently converted to a number of optically pure cyclic frameworks with versatile scaffold diversity as shown in Scheme 6.

Scheme 6



Shi *et al*[12] developed a novel bis(thio)urea organocatalyst (**15**) was synthesized from axially chiral (R)-(-)-5,5',6,6',7,7',8,8'-octahydro-1,1'-2,2'-diamine (H_8-BINAM), and its catalytic ability has been examined in the Morito-Baylis-Hillman reaction of 2-cyclohexen-1-one or 2-cyclopenten-1-one with a wide range of aromatic aldehydes in combination with DABCO. The best result was achieved in the reaction of 3-fluorobenzaldehyde with 2-cyclohexen-1-one to give the desired Morita-Baylis- Hillman products in 79% yield and 88% ee as shown in Scheme 7.

Scheme 7



CONCLUSION

Asymmetric synthesis of enantioselective pure heterocyclic and allylic compounds using different type asymmetric catalyst from Baylis-Hillman derivatives. Therefore, several methodologies have been developed in recent years for the asymmetric synthesis of *γ,γ*-butenolides with MBH carbonates to access *γ,γ*-disubstituted butenolides containing adjacent quaternary and tertiary chiral centers has been presented in excellent stereoselectivities. Chemo- and *α* -regioselective asymmetric Michael addition of *γ,γ*-disubstituted *α,β*-unsaturated aldehydes to nitroolefins has been presented in excellent diastereo- and enantioselectivities (dr up to >99:1, 93-96% ee) via dienamine catalysis. This Focus Review provides an enantioselective pure asymmetric synthesis of from Baylis-Hillman adducts using various asymmetric catalysts.

ACKNOWLEDGMENT

We thank AMET University for the financial support. We also thank Saveetha Engineering College for the financial support.

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