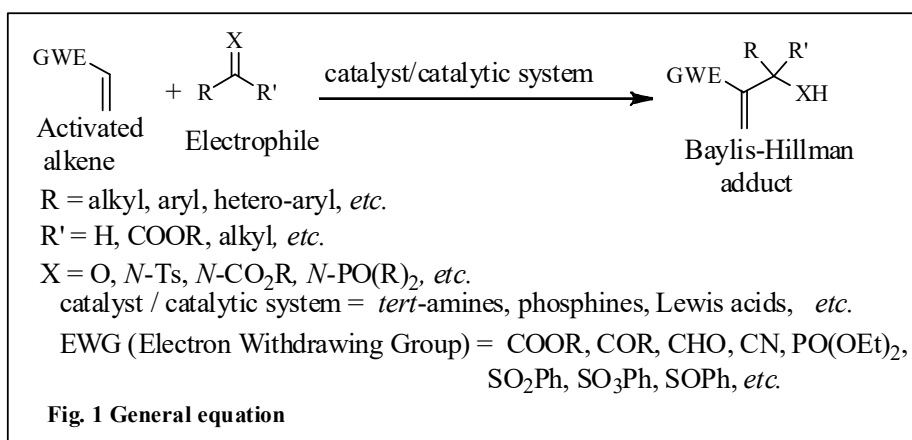


## Non-Amine Catalyzed Baylis-Hillman Reaction

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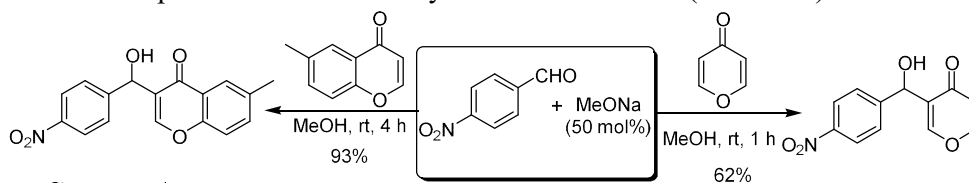
**Introduction:** The synthetic chemistry demands expansion of different carbon-carbon bond forming reactions and has been working in this direction for the last several years. The Baylis-Hillman reaction<sup>1,2</sup> is a carbon-carbon bond forming reaction which is essentially a three-component (electrophile, activated alkene and catalyst) reaction has been developing in recent years. This is an atom economic reaction, coupling at  $\alpha$ -position of activated alkene with carbon electrophile under catalytic influence of a tertiary amine. The most commonly used catalyst is 1,4-diazabicyclo(2.2.2)octane [DABCO] to produce the Baylis-Hillman (B-H) adducts (Fig. 1). The Baylis-Hillman reaction originates from a German patent<sup>3</sup> filed in the year 1972 by two American chemists A. B. Baylis and M. E. D. Hillman. They had also U.S patent<sup>4</sup> in the year 1973 on this reaction.



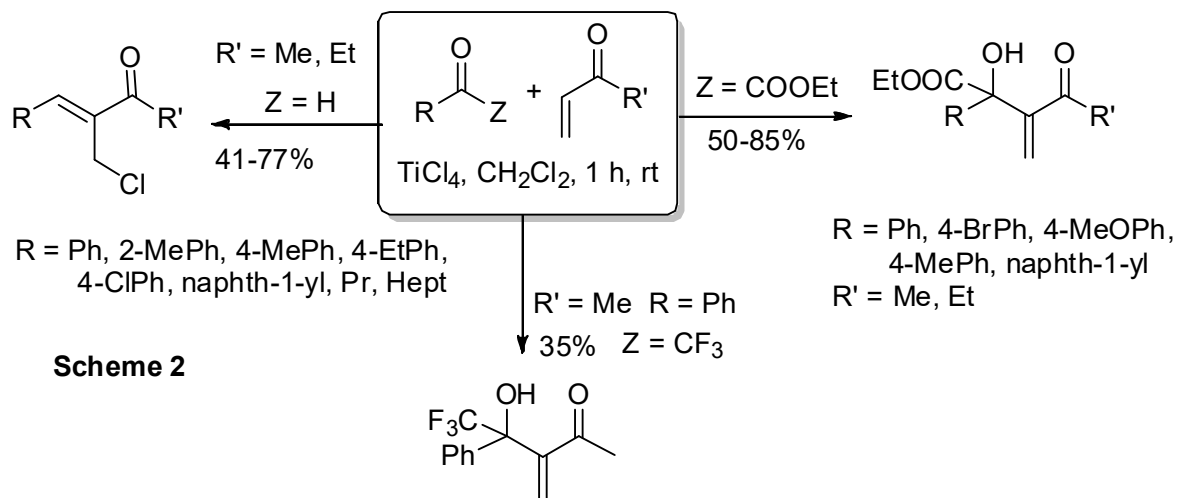
### Non-Amine Catalyzed Baylis-Hillman Reaction:

In addition to the tertiaryamine catalysts, several non-amine catalysts such as trialkylphosphines, triarylphosphines and metal complexes like RhH(PPh<sub>3</sub>)<sub>4</sub>, RuH<sub>2</sub>(PPh<sub>3</sub>)<sub>4</sub>, R<sub>2</sub>S-TiCl<sub>4</sub>, TiCl<sub>4</sub>-NR<sub>4</sub>X (X = halide), TiCl<sub>4</sub>NR<sub>3</sub>, TiCl<sub>4</sub>, and R<sub>2</sub>X-BF<sub>3</sub> (X = O, S) were successfully employed to the coupling of activated alkenes with aldehydes to provide the Baylis-Hillman adducts.

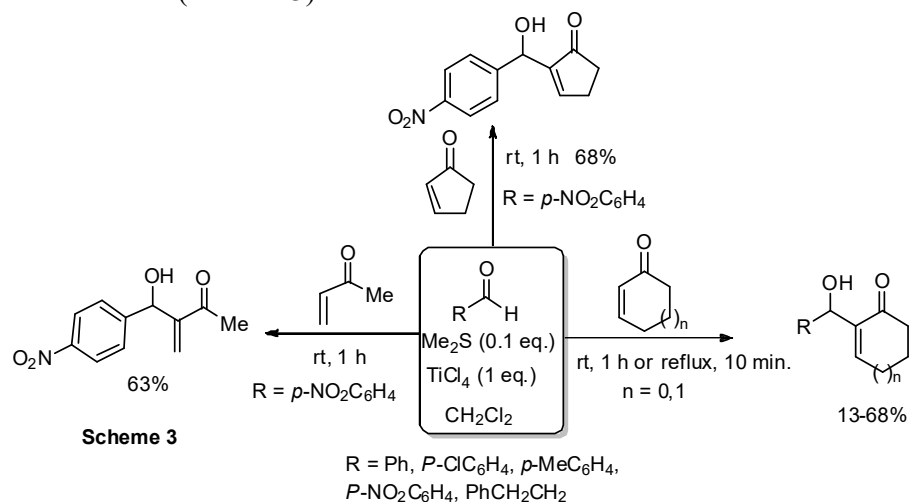
Cheng and coworkers<sup>5</sup> applied, for the first time, methoxide ion as useful catalyst for Baylis-Hillman reaction with cyclic activated alkenes and various aldehydes under mild conditions to provide the desired Baylis-Hillman adducts (Scheme 1).



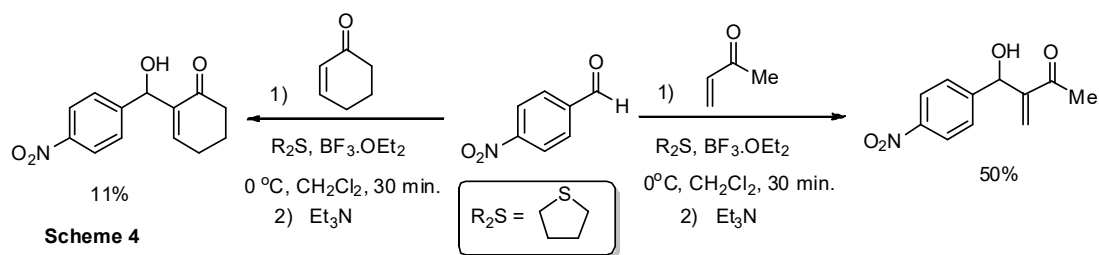
TiCl<sub>4</sub> catalyzed Baylis-Hillman reaction of  $\alpha$ -keto esters and trifluoromethyl phenyl ketone with alkyl vinyl ketones to obtain the desired Baylis-Hillman adducts has been reported by Basavaiah research group.<sup>6</sup> Similar reaction with aldehydes provided the (*Z*)-allyl chlorides (Scheme 2).



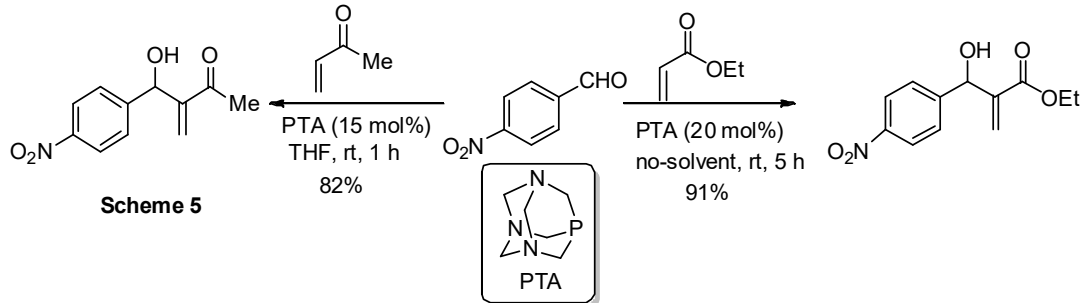
Kataoka and co-workers<sup>7-9</sup> reported an interesting class of chalcogenide catalyzed Baylis-Hillman reaction of various aldehydes with alkyl vinyl ketones in the presence of titanium tetrachloride (Scheme 3).



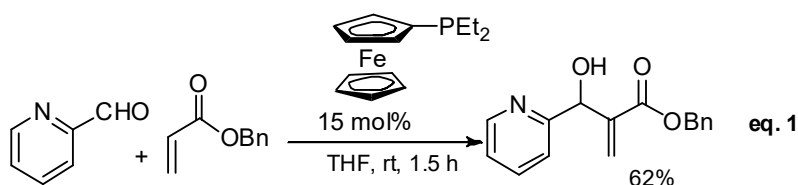
Goodman and co-workers<sup>10</sup> have applied tetrahydrothiophene  $\text{BF}_3 \cdot \text{OEt}_2$  as a catalytic system for the Baylis-Hillman coupling between aldehydes (electrophiles) and activated ketones (MVK and cyclohex-2-enone) (Scheme 4).



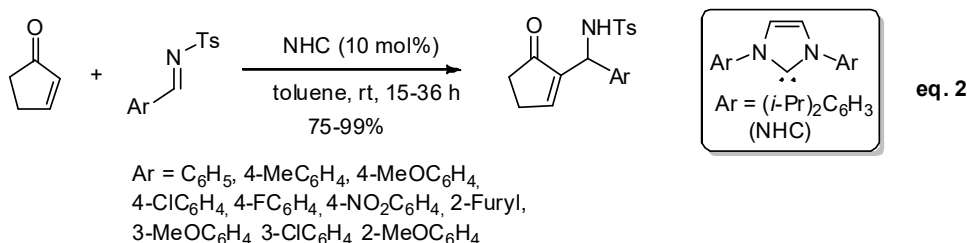
1, 3, 5-Triaza-7-phosphaadamantine (PTA) has been successfully employed as a catalyst for the Baylis-Hillman reaction of various aldehydes with various activated olefins by He and co-workers<sup>11</sup> (Scheme 5).



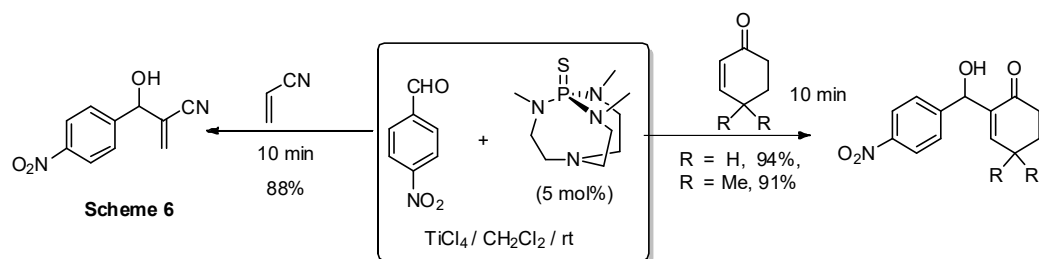
Ferrocene diethylphosphine as an air stable catalyst reported by Carretero and co-workers<sup>12</sup> for the Baylis-Hillman coupling reaction of various aldehydes and acrylates to obtain the corresponding B-H adducts in high yields (eq. 1).



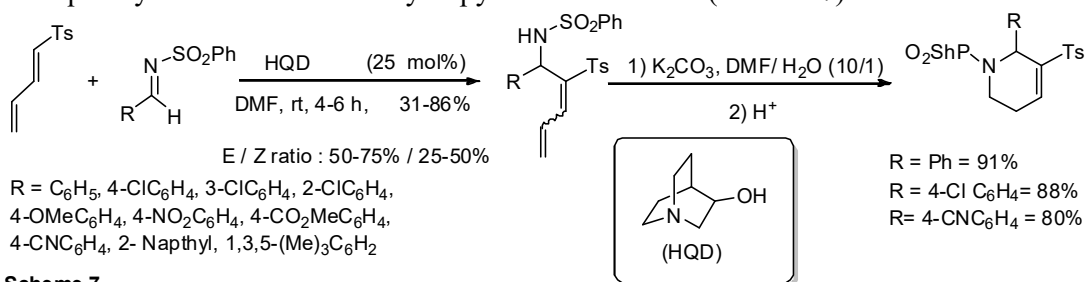
*N*-heterocyclic carbene (NHC) catalyzed Baylis-Hillman reaction of cyclic enones with a *N*-tosylimines has been reported by He and co-workers<sup>13</sup> to obtain the corresponding B-H adducts in high yields (eq.2).



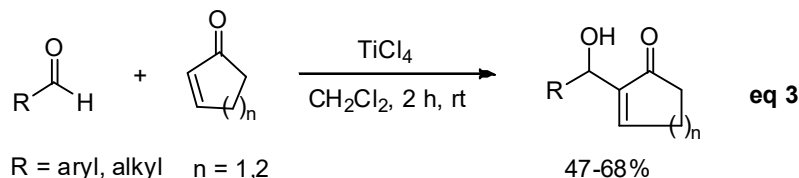
The aza-phosphine has been used as a catalyst for the Baylis-Hillman coupling between various acyclic/cyclic activated alkenes and different types of aldehydes by Verkade and co-workers<sup>14</sup> in high yields (Scheme 6).



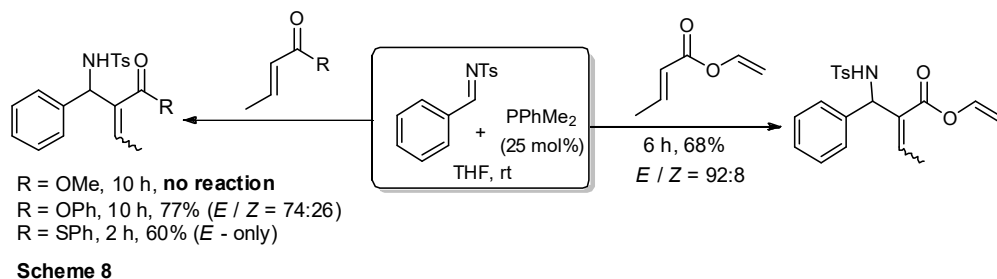
Back and co-workers<sup>15</sup> have successfully employed (*p*-toluenesulfonyl)-1,3-butadiene as activated alkene for coupling with aldimine derivatives. 3-Hydroxyquinuclidine (HQD) applied as catalyst to provide the corresponding Baylis-Hillman adducts which were subsequently converted into tetrahydropyridine derivatives (Scheme 7).



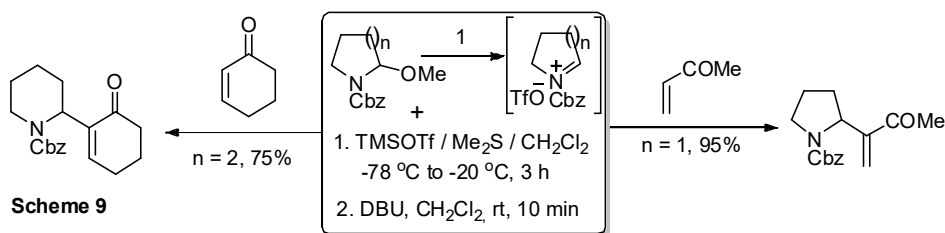
$\text{TiCl}_4$ -mediated Baylis-Hillman reaction of cyclic enones with various aldehydes reported by Li and co-workers<sup>16</sup>(eq3).



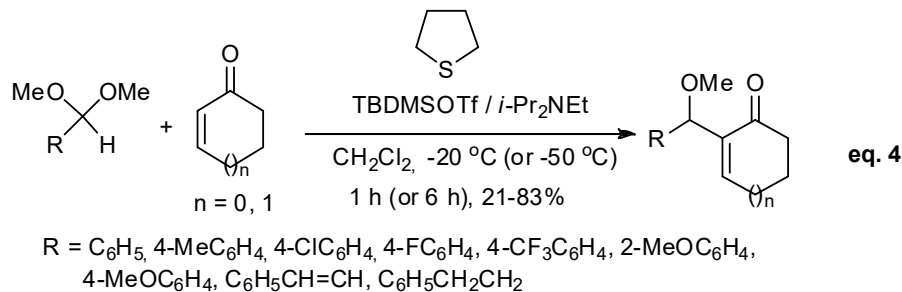
Shi *et al.*, reported phosphine ( $\text{PPhMe}_2$ ) catalysed *aza*-Baylis-Hillman reaction of  $\beta$ -substituted  $\alpha$ ,  $\beta$ -unsaturated esters with *N*-tosylated imines to provide the corresponding Baylis-Hillman adducts (Scheme 8).<sup>17</sup>



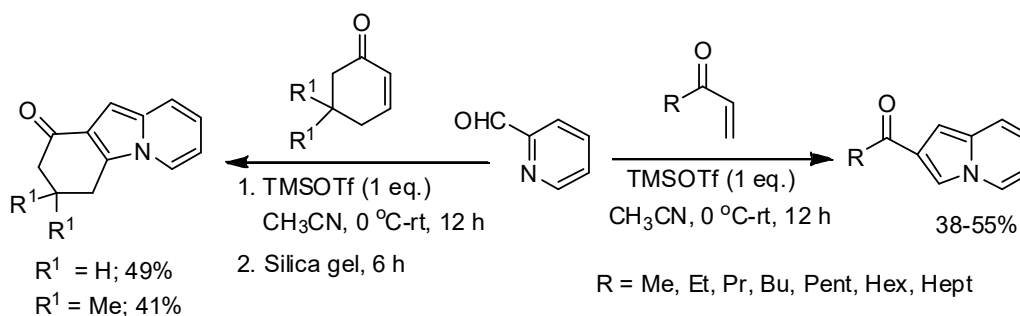
*In situ* generated iminium ions as electrophiles to produce the Baylis-Hillman adduct with activated alkenes reported by Aggarwal and coworkers<sup>18</sup>(Scheme 9).



Metzner and coworkers<sup>19</sup> have used dimethyl acetals as electrophiles with cyclic enones in the Baylis-Hillman coupling under the influence of tetrahydrothiophene and TBDMSOTf in the presence of *i*-Pr<sub>2</sub>NEt (Hunig's base) (eq. 4).

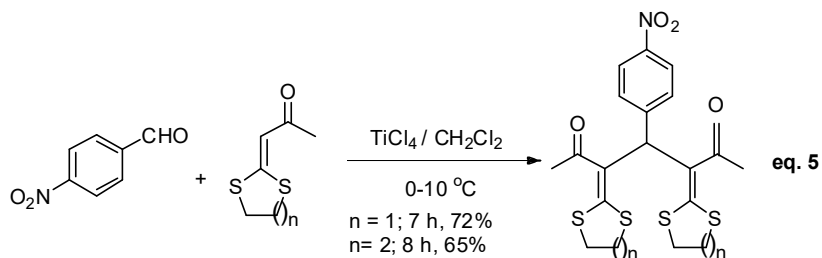


Basavaiah research group published an electrophile induced intramolecular Baylis-Hillman reaction between activated alkenes and pyridine-2-carboxaldehyde under the influence of trimethylsilyl trifluoromethanesulfonate (TMSOTf), for the synthesis of indolizine (Scheme 10).<sup>20</sup>

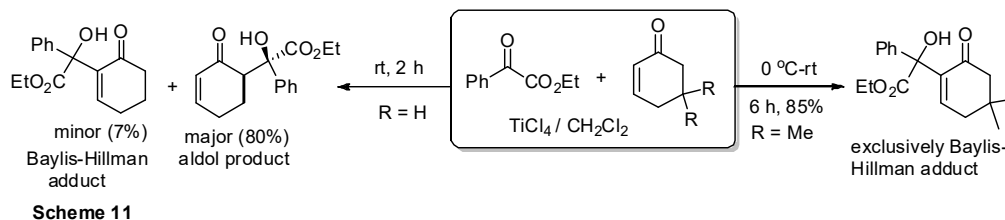


**Scheme 10**

Yin and coworkers<sup>21</sup> published, TiCl<sub>4</sub>-mediated Baylis-Hillman type reaction of  $\alpha$ -oxoketene dithioacetals with aldehydes for the synthesis of polyfunctionalized 1,4-pentadienes *via* C-C bond formation at the  $\alpha$ -position of  $\alpha$ -oxoketene dithioacetals has been described (eq. 5).

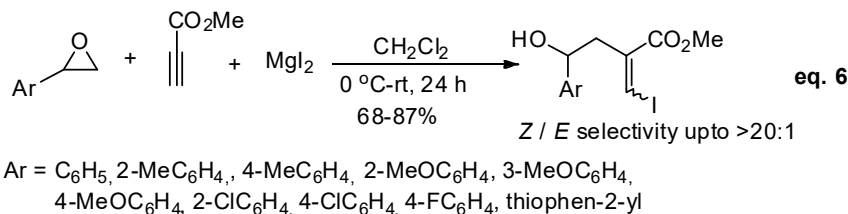


Basavaiah research group<sup>22</sup> has developed steric factors directed Baylis-Hillman and aldol reactions in TiCl<sub>4</sub> mediated coupling between  $\alpha$ -keto esters with cyclohex-2-enone derivatives. Thus, 5,5-dimethylcyclohex-2-enone provides the corresponding Baylis-Hillman adducts exclusively in reaction with  $\alpha$ -keto esters under the influence of TiCl<sub>4</sub>, whereas a similar reaction of  $\alpha$ -keto esters with cyclohex-2-enone furnishes the corresponding aldol adducts with high *syn*-diastereoselectivity as the major product along with the Baylis-Hillman adduct as the minor product (Scheme 11).

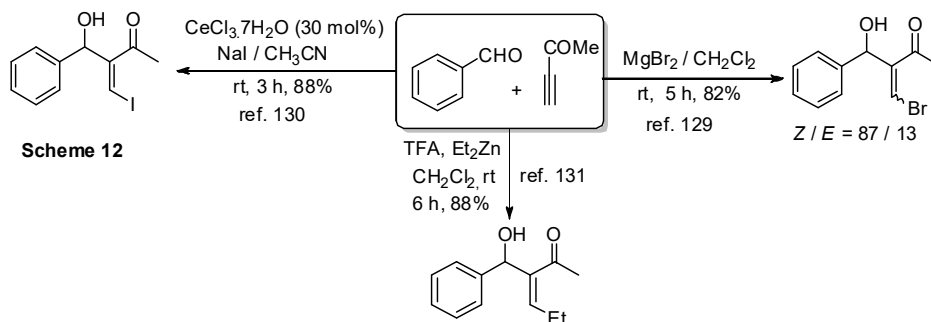


**Scheme 11**

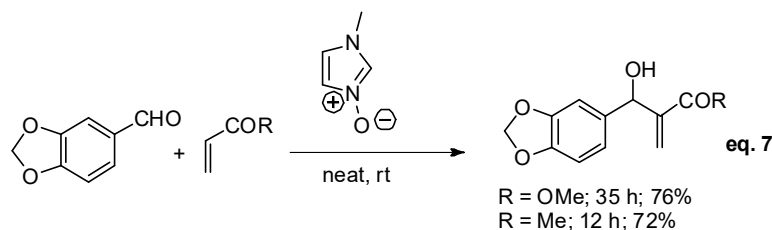
For the first time, Li and coworkers<sup>23</sup> demonstrated the application of oxirane as an electrophile for coupling with methyl propiolate in the presence of  $MgI_2$  to provide densely functionalized homoallylic alcohols (eq. 6).



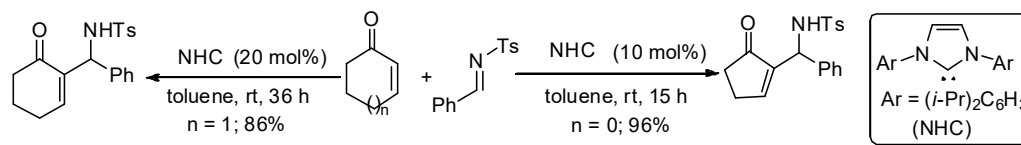
Various research groups<sup>24-26</sup> developed independently simple methods for synthesis of  $\beta$ -substituted Baylis-Hillman adducts *via* one-pot three-component reaction protocol involving the treatment of  $\alpha$ ,  $\beta$ -acetylenic ketones (*in situ* generation of allenolates) with various aldehydes in the presence of various catalysts / reagents to provide allyl alcohols (Scheme 12).



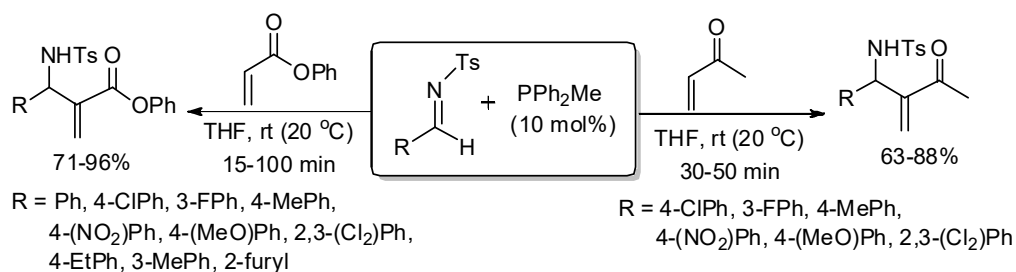
1-Methylimidazole 3-*N*-oxide catalyzed Baylis-Hillman coupling of various aldehydes with methyl acrylate / methyl vinyl ketone to provide corresponding adducts in good yields was reported by Tsai and coworkers (eq. 7).<sup>27</sup>



Ye and coworkers<sup>28</sup> described an interesting, *N*-heterocyclic carbene (NHC) catalyzed aza-Baylis-Hillman coupling of cyclic enones with a variety of *N*-tosylimines to provide the corresponding adducts in high yields (Scheme 13).

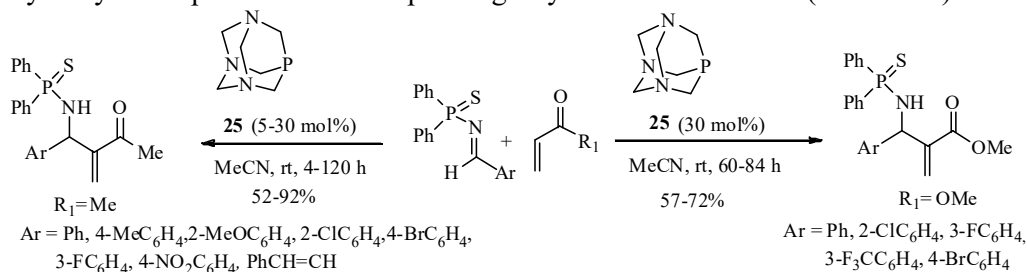


Shi and Xu<sup>29</sup> have successfully used methyl diphenylphosphine as a catalyst for Baylis-Hillman reaction between *N*-tosylated imines and different activated olefins (Scheme 14).



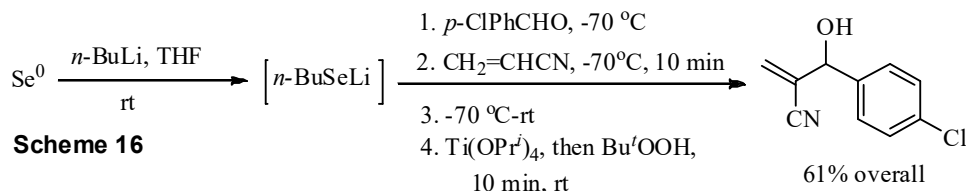
Scheme 14

Zhou and coworkers<sup>30</sup> have described an interesting 1,3,5-triaza-7-phosphaadamantane (PTA) catalyzed Baylis-Hillman coupling of *N*-thiophosphoryl imines with MVK and methyl acrylate to provide the corresponding Baylis-Hillman adducts (Scheme 15).



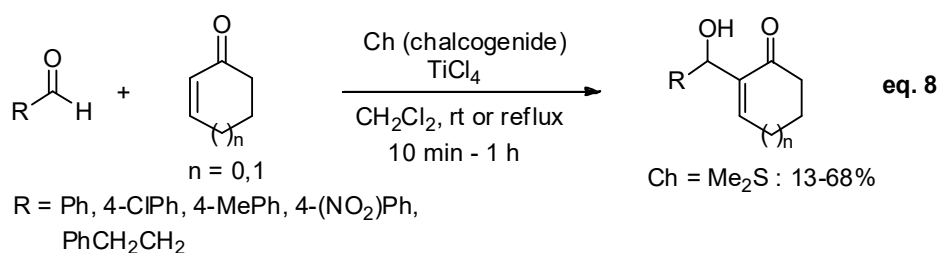
Scheme 15

Comasseto and coworkers<sup>31</sup> have established a simple and efficient one-pot access to Baylis-Hillman adducts (Scheme 16).

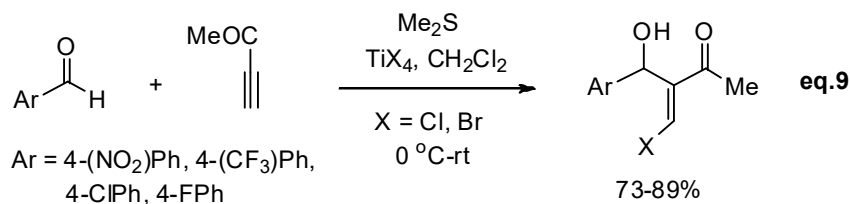


Scheme 16

Kataoka *et al.*<sup>32</sup> have developed an interesting Baylis-Hillman coupling of vinyl ketones with various aldehydes catalyzed by sulfides or selenides (Me<sub>2</sub>S, PhSMe) in the presence of TiCl<sub>4</sub> as a Lewis acid. Selenide and Me<sub>2</sub>S were proved to be the best catalysts for this reaction (eq. 8).



Kataoka<sup>33</sup> successfully reported chalcogeno-Baylis-Hillman reaction to activated alkynes. Thus, the reaction between activated alkynes with aldehydes under the influence of Me<sub>2</sub>S.TiX<sub>4</sub> provided an interesting  $\alpha$ -halomethylene aldols *i.e.*,  $\beta$ -halo Baylis-Hillman adducts (eq. 9).



### References:

1. Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed; New York: Wiley, 1997; Vol. 51, p 201.
2. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811.
3. Baylis, A. B.; Hillman, M. E. D. German patent 2155113, 1972; *Chem. Abstr.* **1972**, *77*, 34174q.
4. Hillman, M. E. D.; Baylis, A. B. U.S. Patent 3,743,669, 1973
5. Luo, S.; Mi, X.; Xu, H.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 8413.
6. Basavaiah, D.; Sreenivasulu, B. Mallikarjuna Reddy, R.; Muthukumaran, K.; *Synth. Commun.* **2001**, *31*, 2987
7. Kataoka, T.; Iwama, T.; Tsujiyama, S.-i.; Iwamura, T.; Watanabe, S.-i. *Tetrahedron* **1998**, *54*, 11813.
8. Iwama, T.; Kinoshita, H.; Kataoka, T. *Tetrahedron Lett.* **1999**, *40*, 3741.
9. Kataoka, T.; Kinoshita, H.; Iwama, T.; Tsujiyama, S.-i.; Iwamura, T.; Watanabe, S.-i.; Muraoka, O.; Tanabe, G. *Tetrahedron* **2000**, *56*, 4725.
10. Walsh, L. M.; Winn, C. L.; Goodman, J. M. *Tetrahedron Lett.* **2002**, *43*, 8219.
11. He, Z.; Tang, X.; Chen, Y.; He, Z. *Adv. Synth. Catal.* **2006**, *348*, 413.
12. Pereira, S. I.; Adrio, J.; Silva, A. M. S. Carretero, J. C. *J. Org. Chem.* **2005**, *70*, 10175.
13. He, L.; Jain, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466.
14. You, J.; Xu, J.; Verkade, J. G. *Angew. Chem. Int. Ed.* **2003**, *42*, 5054.
15. Back, T. G.; Rankic, D. A.; Sorbetti, J. M.; Wulff, J. E. *Org. Lett.* **2005**, *7*, 2377.
16. Li, G.; Wei, H.-X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1.
17. Shi, Y.-L.; Shi, M. *Tetrahedron* **2006**, *62*, 461.
18. Myers, E. L.; deVries, J. G.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2007**, *46*, 1.
19. Srivardhana Rao, J.; Briere, J.-F.; Metzner, P.; Basavaiah, D. *Tetrahedron Lett.* **2006**, *47*, 3553.
20. Basavaiah, D.; Jaganmohan Rao, A. *Chem. Commun.* **2003**, 604.
21. Yin, Y.-B.; Wang, M.; Liu, Q.; Hu, J.-L.; Sun, S.-G.; Kang, J. *Tetrahedron Lett.* **2005**, *46*, 4399.
22. Basavaiah, D.; Sreenivasulu, B.; Jaganmohan Rao, A. *J. Org. Chem.* **2003**, *68*, 5983.
23. Kattuboina, A.; Kaur, P.; Timmons, C.; G. Li, *Org. Lett.* **2006**, *8*, 2771.
24. Wei, H.-X.; Jasoni, R. L.; Hu, J.; Li, G.; Pare, P. W. *Tetrahedron* **2004**, *60*, 10233.
25. Yadav, J. S.; Reddy, B. V. S.; Gupta, M. K.; Eeshwaraiiah, B. *Synthesis* **2005**, 57.
26. Xue, S.; He, L.; Han, K.-Z.; Liu, Y.-K.; Guo, Q.-X. *Synlett* **2005**, 1247.
27. Lin, Y.-S.; Liu, C.-W.; Tsai, T. Y. R. *Tetrahedron Lett.* **2005**, *46*, 1859.
28. He, L.; Jain, T.-Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466.
29. Xu, Y.-M.; Shi, M. *J. Org. Chem.* **2004**, *69*, 417.
30. Xu, X.; Wang, C.; Zhou, Z.; Tang, X.; He, Z.; Tang, C. *Eur. J. Org. Chem.* **2007**, 4487.
31. Keppler, A. F.; Gariani, R. A.; Lopes, D. G.; Comasseto, J. V. *Tetrahedron Lett.* **2009**, *50*, 2181.
32. Kataoka, T.; Iwama, T.; Tsujiyama, S.-i. *Chem. Commun.* **1998**, 197.
33. Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watanabe, S.-i. *Angew. Chem. Int. Ed.* **2000**, *39*, 2358.

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