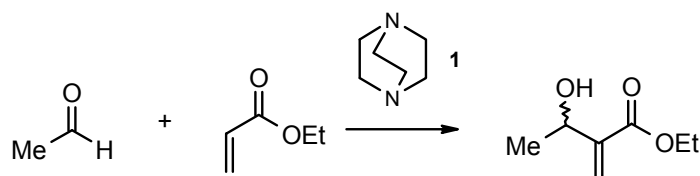


The Asymmetric Baylis-Hillman Reaction

The Baylis-Hillman reaction has roots back to 1968, when Morita described the reaction of an aldehyde with acrylic compounds catalyzed by tricyclohexylphosphine.¹ He named the transformation "Carbinol Addition." However, the yield of the reaction was extremely poor (20%).

In 1972, Anthony Baylis and Melville Hillman from the Celanese Corporation were granted a German patent for performing the same reaction using a tertiary amine catalyst instead of a phosphine catalyst (Scheme 1).² In the patent, they reported yields of 75% after one week. They reported their most successful catalyst to be DABCO (1,4-diazabicyclo[2.2.2]octane) (**1**). It would be sixteen years later, when the transformation was named the Baylis-Hillman Reaction.

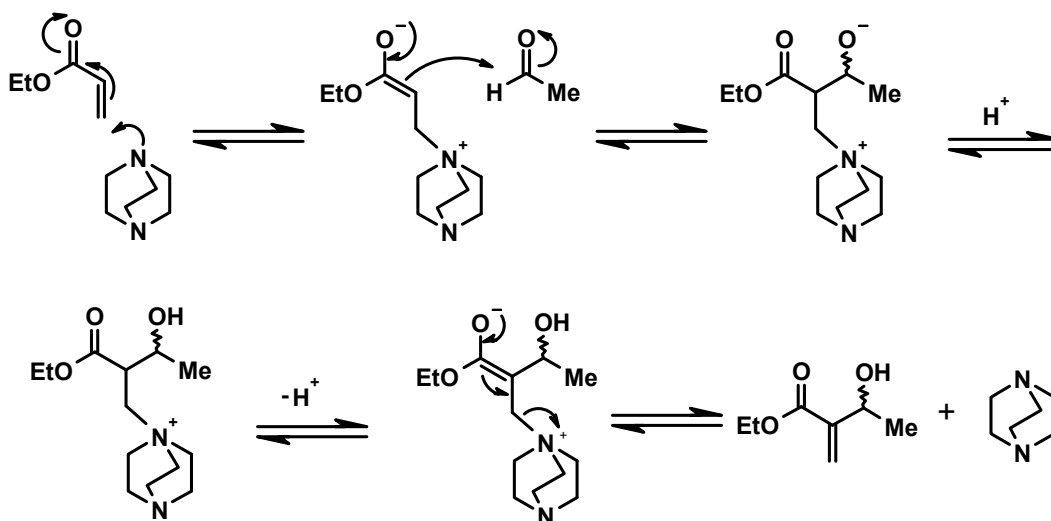
Scheme 1



In 1983, the reaction was rediscovered, and its scope was explored primarily by Drewes and Basavaiah.³ Since that time, the scope of the reaction has broadened past using just aldehydes and acrylates.⁴ Alkyl vinyl ketones, acrylonitriles, vinyl sulfones, acrylamides, allenic esters, vinyl sulfonates, vinyl sulfoxides, vinyl phosphonates, and acroleins have been substituted for the acrylate component.⁴ Imines, tosylimines, α -ketoesters, fluoroesters, and π -deficient olefins have been used in addition to aldehydes.⁴

The accepted mechanism differs very little from that originally proposed by Morita and is supported mainly by kinetic studies (Scheme 2).^{5,6} It should be noted that none of the zwitterionic intermediates have been isolated to date.

Scheme 2



The main drawback of the Baylis-Hillman reaction is the extremely slow reaction rate. The reaction can take from days to weeks to complete. Numerous efforts have been made towards the development of different catalytic systems.

Aggarwal and coworkers reported that by increasing the basicity and consequently the nucleophilicity of the amine catalyst, the rate is substantially increased.⁷ They also reported that the addition of a weak Lewis acid, such as La(OTf)₃, can increase the rate up to thirty fold.⁸ Later, Kataoka reported that a stronger Lewis acid such as TiCl₄ can be used with a weak nucleophilic catalyst such as dimethyl sulfide.⁹

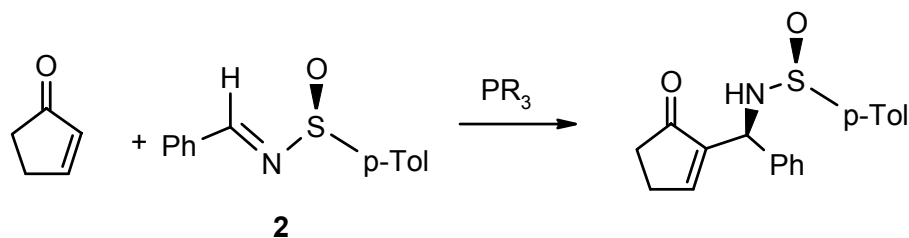
The Asymmetric Baylis-Hillman Reaction:

The traditional Baylis-Hillman reaction consists of three components: an electrophile, a π -deficient alkene, and a nucleophilic catalyst. Any component can be used to influence the stereochemistry at the newly formed stereogenic carbon.

Optically Active Electrophile:

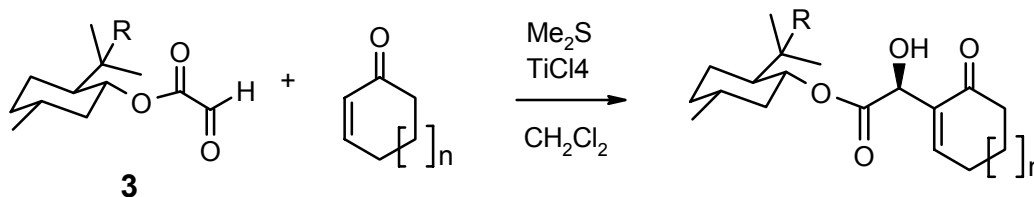
To date, using optically active electrophiles in the Baylis-Hillman reaction has seen only moderate success. Shi *et al.* used trialkylphosphines to catalyze the reaction between optically active *N*-sulfinimines **2** and cyclopentenone to give products with good yields and good diastereoselectivities (Table 1).¹⁰ Their best conditions (PhPMe₂, toluene) gave yields that ranged from 70-80% with diastereoselectivities between 75 and 85% for a wide variety of *N*-sulfinimines.

Table 1



Solvent	PR ₃	% Yield	% <i>de</i>
Toluene	PBu ₃	69	68
Toluene	PhPMe ₂	72	82
THF	PBu ₃	67	70
THF	PhPMe ₂	85	50

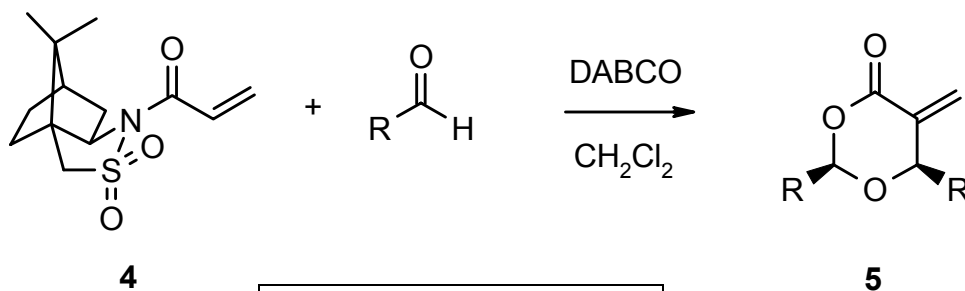
The most impressive selectivities using an optically active electrophile come from the Bauer lab at Warsaw University.¹¹ They used chiral glyoxylates **3** derived from menthol and 8-phenylmenthol (Table 2) and found that the sterically more demanding 8-phenylmenthol group not only gave higher yields (76%), but also provided excellent diastereoselectivities (>95%) under Kataoka conditions.

Table 2

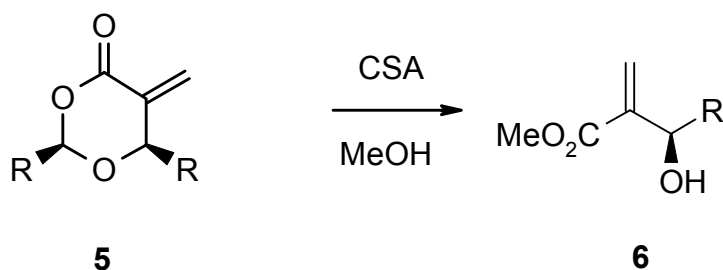
R	n	% Yield	% <i>de</i>
H	1	45	8.7
Ph	1	78	>95
Ph	0	76	>95

Optically Active π -Deficient Olefins:

The combination of chiral auxiliaries with activated olefins has led to the greatest degree of success in Asymmetric Baylis-Hillman reaction. The most prominent example is the use of camphor derived sultam **4** by Leahy (Table 3).¹² By using a second equivalent of aldehyde, the chiral auxiliary can be fortuitously cleaved from the product *in situ* to give an optically active dioxanone **5** in good yields and excellent stereoselectivities. This method is effective for unbranched aliphatic aldehydes. α -Branched aldehydes give lower yields, while aromatic aldehydes are unreactive. With treatment of mild acid or base, the dioxanone can be converted to the target Baylis-Hillman adduct **6** (Scheme 3).

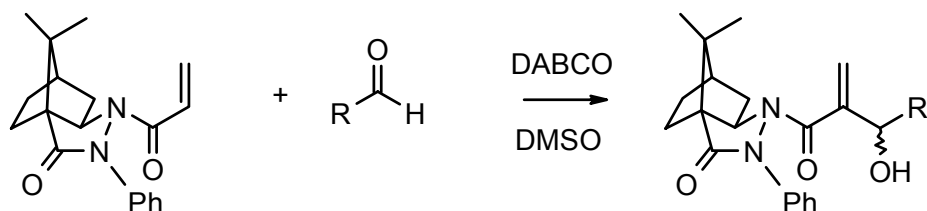
⁴**Table 3**

R	% Yield	% <i>ee</i>
Me	85	>99
Et	98	>99
<i>i-Pr</i>	33	>99
Ph	0	-

Scheme 3

Chen's lab provided a related example to Leahy's work (Table 4).¹³ Instead of using a camphor-derived sultam, they used hydrazide **7**. Three main differences were encountered with the hydrazide auxiliary. First, with the inclusion of a second equivalent of aldehyde, the auxiliary was not cleaved. Secondly, aromatic aldehydes were able to react when DMSO was used as a solvent. Most importantly, the reaction showed remarkable solvent dependence. When DMSO was used, the configuration at the new stereogenic carbon was *S*. When aqueous THF was used, the selectivity reversed. The exact role of the solvent is unknown and is under investigation.

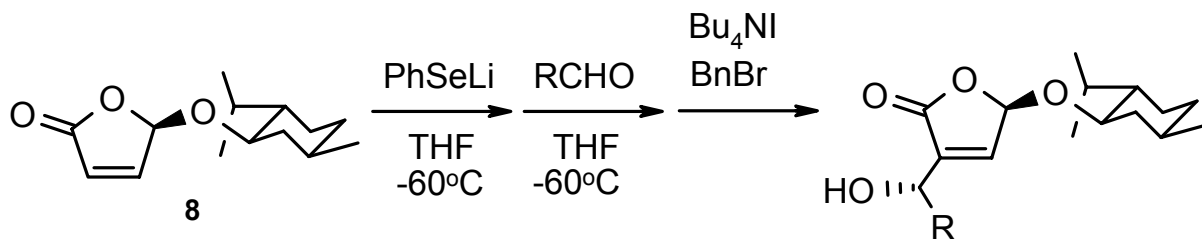
Table 4



R	configuration	% Yield	% <i>de</i>
Me	<i>S</i>	88	94
Et	<i>S</i>	85	98
Ph	<i>S</i>	80	98
Me	<i>R</i>	73	94
Et	<i>R</i>	85	98
Ph	-	0	-

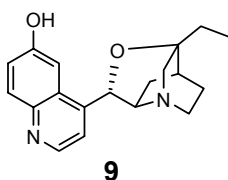
Jauch's approach involved using 4-methoxy-butenolide **8** (Table 5).¹⁴ This olefin proved to be unreactive when DABCO was used as the catalyst, therefore, the stronger nucleophile lithium phenylselenide was used. The selenide would add in a Michael fashion to the α,β unsaturated lactone. The resulting enolate would attack the aldehyde with the resulting stereochemistry being predicted by a Zimmerman-Traxler transition state. The selenide then can be eliminated by alkylating with benzyl bromide or simply warming the reaction temperature from -60°C to -20°C . Excellent yields and excellent diastereoselectivities were reported with this method.

Table 5



R	% Yield	% <i>de</i>
Ph	82	>99
<i>i</i> -Pr	89	>99
<i>t</i> -Bu	67	>99

Optically Active Catalyst:



The holy grail of the asymmetric Baylis-Hillman lies in an efficient, general catalyst that can be recovered and reused. Almost all of the chiral catalysts applied to the Baylis-Hillman reaction have been plagued with low yields or low selectivities. Hatakeyama has developed the best catalyst to date.¹⁵ Amine **9** is a derivative of quinidine that gives moderate yields and high selectivities.

Unfortunately, this catalyst is still very substrate dependent. To react with a wide variety of aldehydes in a highly enantioselective manner, an activated acrylate such as hexafluoroisopropylacrylate **10** is used (Table 6).

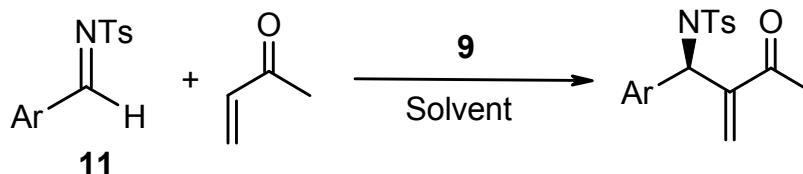
Table 6



R	% Yield	% ee
Ph	57	95
Et	40	97
<i>i</i> -Pr	36	99
Ph	31	99
<i>t</i> -Bu	0	-

Shi and coworkers have shown that methyl vinyl ketone and methyl acrylate could be used with the same catalyst to generate similarly high selectivity if aryl tosylimines **11** were used as the electrophiles (Table 7).¹⁶

Table 7

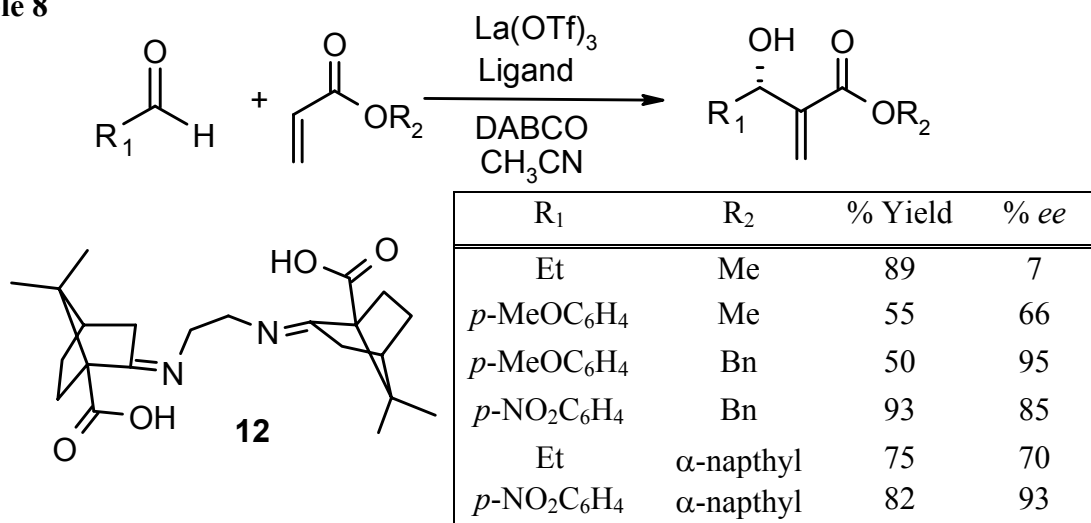


Ar	Solvent	% Yield	% ee
<i>p</i> -EtC ₆ H ₄	DMF	55	93
<i>p</i> -EtC ₆ H ₄	MeCN	64	86
<i>p</i> -EtC ₆ H ₄	DMF/MeCN	74	96
<i>p</i> -ClC ₆ H ₄	DMF	51	95
<i>p</i> -ClC ₆ H ₄	MeCN	80	81
<i>p</i> -ClC ₆ H ₄	DMF/MeCN	68	93

Optically Active Lewis Acid:

From Aggarwal's work, it was possible to use the addition of a chiral Lewis acid catalyst to influence the enantioselectivity of the Baylis-Hillman reaction. Chen and coworkers developed an additive **12** that gave good yields and selectivities when used in conjunction with DABCO and La(OTf)₃ (Table 8).¹⁷ This method had the greatest success when α -naphthyl acrylate and aromatic aldehydes were used.

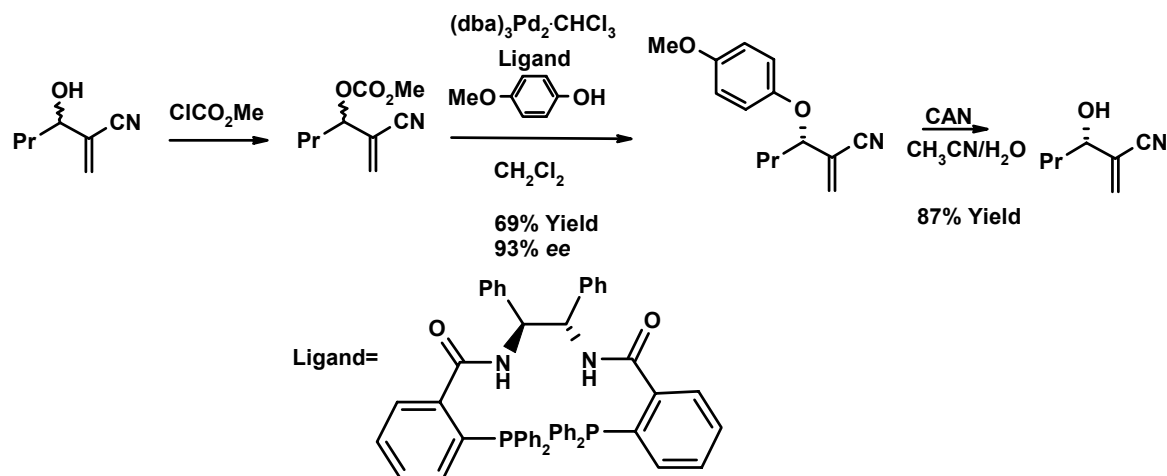
Table 8



Deracemization:

Trost *et al.* developed a dynamic kinetic asymmetric transformation (DYKAT) for the Baylis-Hillman that he calls a "deracemization" (Scheme 4).¹⁸ With this protocol, he is able to convert a racemic mixture of Baylis-Hillman adducts into a single enantiomer. The key step involves the formation of an asymmetric Pd π -allyl complex that is replaced by a nucleophile. Finally, the nucleophile is converted to a hydroxyl group.

Scheme 4



Conclusion:

Several advances in the Baylis-Hillman reaction have been made in the past five years. The scope has been greatly broadened, and the reaction times have been reduced. There still remains much work to be done towards developing a general protocol for the Asymmetric Baylis-Hillman reaction. Using chiral auxiliaries on activated alkenes has shown the most promise. Either enantiomer can be accessed by switching the auxiliary in Leahy's case or simply changing the solvent in Chen's example. The method shows little reactivity when aromatic aldehydes are used, though.

The catalytic Asymmetric Baylis-Hillman reaction using the quinidine derivative **9** serves to complement the chiral auxiliary approach. It gives relatively low selectivity with aliphatic aldehydes, but provides excellent selectivity with aromatic aldehydes. Unfortunately, only the *R* enantiomer is currently available through this route.

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