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Aza-Baylis–Hillman Reactions and Their Synthetic Applications

Yong-Ling Shi[a] and Min Shi*[a]

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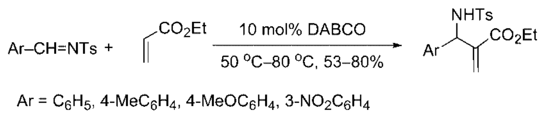
Aza-Baylis–Hillman reactions have attracted much attention over the past decade. This review concentrates on discussion of the origins of and progress in aza-Baylis–Hillman reactions, including the development of catalysts and substrate scopes, mechanistic study, asymmetric reactions, and further transformations of the products.

Introduction

As one of the most important tools for converting simple starting materials into densely functionalized products in a catalytic and atom-economic way, the Baylis–Hillman reaction has made great progress since it was first reported in a patent in 1972.[1] Because of the great potential of its products for further transformation, and also its superior mild reaction conditions, the use of imines as electrophiles in the Baylis–Hillman reactions is extremely fascinating. While the "aza-Baylis–Hillman reaction" strictly refers to the reaction between an azodicarboxylate and an activated alkene to create a carbon–nitrogen bond, from a different point of view the aza-Baylis–Hillman reaction could also be seen as the use of "an activated imine as an electrophile in the Baylis–Hillman reaction". This review summarizes the origins of and advances in the aza-Baylis–Hillman reaction.

Scope of the Reaction

In 1984, Perlmutter and Teo reported that *N*-tosyl imines reacted with ethyl acrylate in the presence of DABCO as catalyst in a sealed tube to give adducts in moderate to good yields;[2] these were the first examples of aza-Baylis–Hillman reactions (Scheme 1).



Scheme 1.

In 2002 our group screened different catalysts in the reactions between *N*-tosyl imines and methyl vinyl ketone.[3] With PPh_3 catalysis, the reactions proceeded smoothly to

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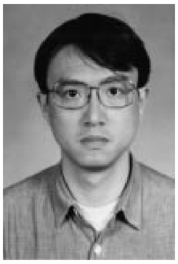
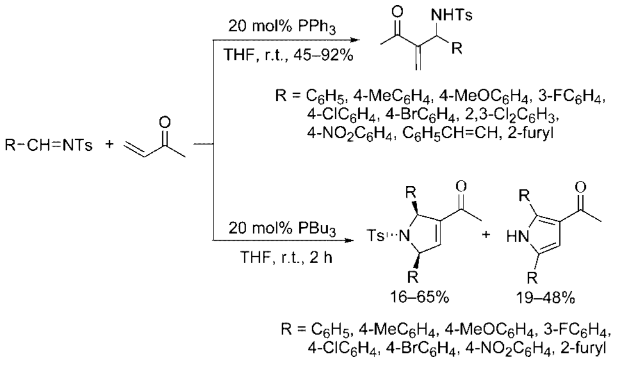


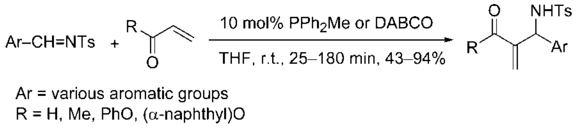
Min Shi was born in Shanghai, China. He received his B.S. in 1984 (Institute of Chemical Engineering of East China) and his Ph.D. in 1991 (Osaka University, Japan). He did postdoctoral research work with Prof. Kenneth M. Nicholas at the University of Oklahoma (1995–1996) and worked as an ERATO Researcher at the Japan Science and Technology Corporation (JST) (1996–1998). He is currently a group leader at the State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences (SIOC, CAS).

give the aza-Baylis–Hillman adducts in moderate to excellent yields, while use of the more nucleophilic PBu_3 as catalyst resulted in two types of cyclized products (Scheme 2).



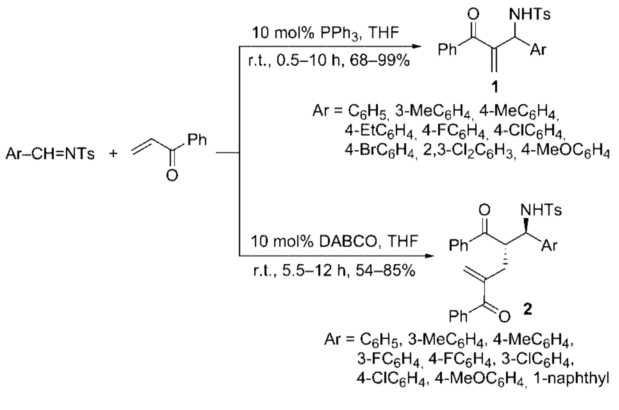
Scheme 2.

Later on, we found that reactions between *N*-tosyl imines and acrolein or acrylates also yielded aza-Baylis–Hillman adducts in moderate to excellent yields in fairly short reaction times with catalysis by PPh_2Me or DABCO (Scheme 3).[4]



Scheme 3.

Interesting results were observed in reactions between *N*-tosyl imines and phenyl vinyl ketone.[5] Use of PPh_3 as the catalyst produced the normal aza-Baylis–Hillman adducts **1**, while use of DABCO as the catalyst gave the double aza-Baylis–Hillman adducts **2** as single *anti* isomers (Scheme 4).



Scheme 4.

We subsequently investigated reactions between *N*-tosyl imines and cyclic α,β-unsaturated ketones.[6] We found that the reactions between *N*-tosyl imines and cyclopent-2-en-1-one yielded normal aza-Baylis–Hillman adducts **3** in the presence of DMAP or PBu_3 as catalyst, while the products of *N*-tosyl imines and cyclohex-2-en-1-one depended on the catalyst employed: DMAP resulted in normal aza-Baylis–Hillman adducts **4** and PBu_3 or DBU afforded aza-Diels–Alder products **5** and **6** along with some normal adducts **4**. With DMAP or DBU catalysis, the reactions between *N*-tosyl imines and cyclohept-2-en-1-one gave mixtures of normal aza-Baylis–Hillman adducts **7** and aza-Diels–Alder products **8** and **9**, while in the reactions between *N*-tosyl imines and cyclooct-2-en-1-one, normal aza-Baylis–Hillman adducts were not formed and different aldol-type products were obtained depending upon the catalyst employed (Scheme 5).

In reactions between allenes and *N*-tosyl imines, we found that buta-2,3-dienoates or penta-3,4-dien-2-one reacted with *N*-tosyl imines to yield azetidine derivatives **13** through [2+2] cycloaddition in the presence of DABCO as catalyst,[7] which contrasts with the [3+2] products derived from phosphane catalysts.[8] With DMAP as the catalyst, dihydropyridine products **14** were formed. Ethyl penta-2,3-dienoate reacted with *N*-tosyl imines in the presence of $PPhMe_2$ as catalyst to give the [3+2] cycloaddition products **15** (Scheme 6).[9]

In the presence of DMAP as catalyst, but-3-yn-2-one reacted with *N*-tosyl imines to give the tetrahydropyridine derivatives (Scheme 7).[9]

In reactions between 3-methylpenta-3,4-dien-2-one and *N*-tosyl imines, acyclic products **16** were obtained in the presence of DMAP as catalyst, while in the presence of tributylphosphane as catalyst the reaction followed different pathways to give two types of tetrahydropyridine derivatives **17** and **18** (Scheme 8).[10]

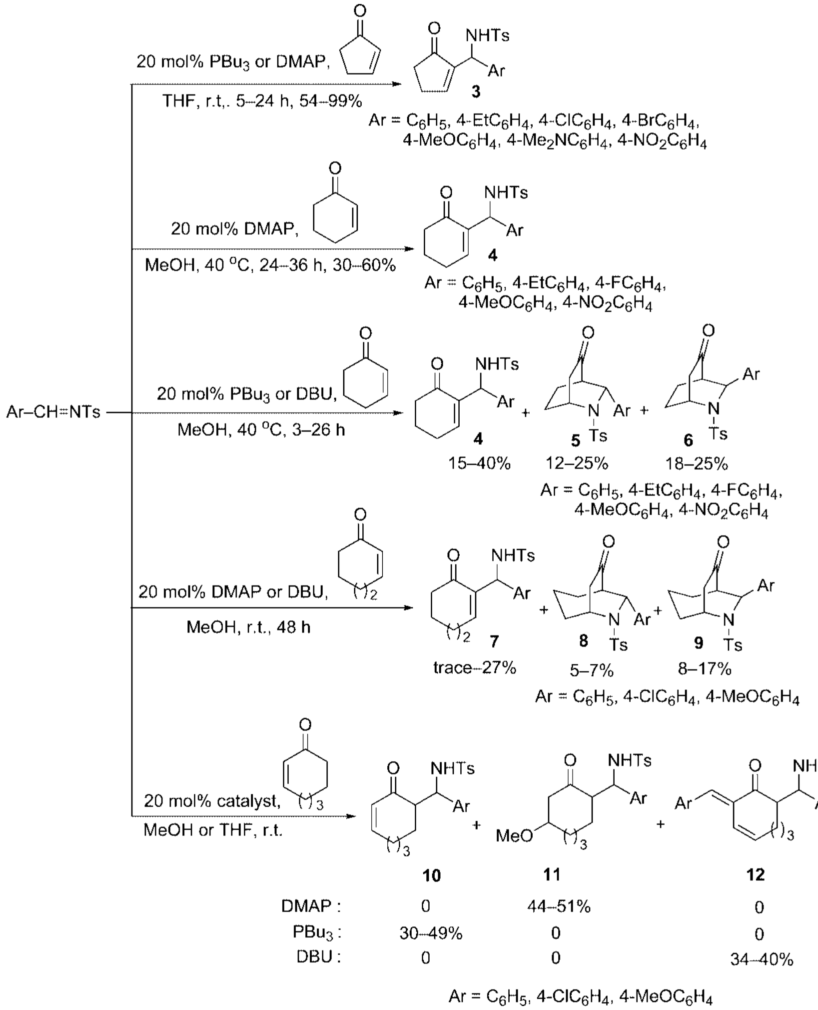
Guo et al. recently reported solvent-free aza-Baylis–Hillman reactions between acrylamide or *N*-arylacrylamide and *N*-tosyl imines with phenol as an additive and DABCO as the catalyst (Scheme 9).[11]

Thanks to their high reactivity as electrophiles, *N*-tosyl imines were found to react with β-substituted electron-deficient alkenes under mild conditions to give the corresponding aza-Baylis–Hillman adducts in moderate to good yields as mixtures of *E*/*Z* isomers (Scheme 10).[12,13]

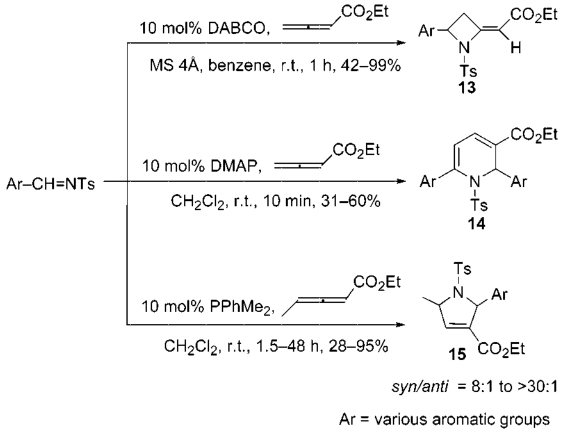
Later on, Back et al. studied the reactions between imines and buta-1,3-diene sulfone.[14] They found that the reactions proceeded smoothly in the presence of 3-HQD as catalyst to give the *E*/*Z* isomeric aza-Baylis–Hillman adducts **19** in moderate to good yields (Scheme 11).

As well as *N*-sulfonyl imines, we also found that *N*-benzylidenediphenylphosphinamides showed high reactivity as electrophiles in aza-Baylis–Hillman reactions.[15,16] In the presence of PPh_3, PPh_2Me, or DABCO as catalyst, the reactions between *N*-benzylidenediphenylphosphinamides and methyl vinyl ketone, acrylates, or acrylonitrile at room temperature gave the normal aza-Baylis–Hillman adducts **20** in moderate to very high yields (Scheme 12).

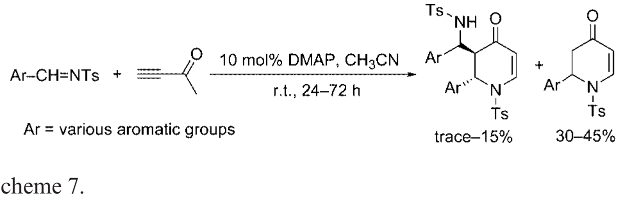
More nucleophilic catalysts such as $PPhMe_2$, PBu_3, or PMe_3 induced reactions between methyl acrylate and *N*-benzylidenediphenylphosphinamides to give double aza-Baylis–Hillman adducts **21** along with the normal adducts



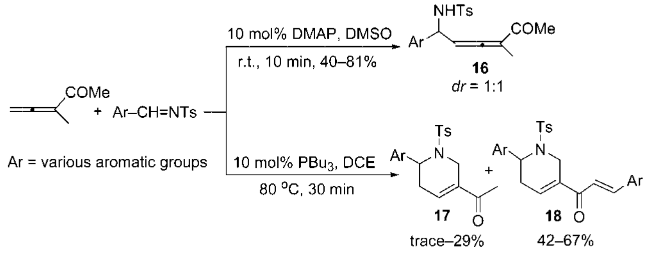
Scheme 5.



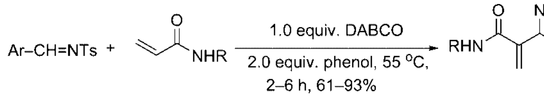
Scheme 6.



Scheme 7.



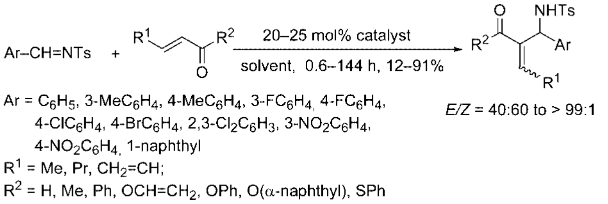
Scheme 8.



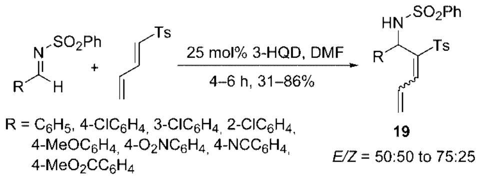
Ar = C_6H_5, 2-HOC_6H_4, 2-ClC_6H_4, 2-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-pyridyl, 4-$MeOC_6H_4$, 2-$NO_2C_6H_4$, 4-FC_6H_4, 3,5-$(MeO)_2C_6H_3$,
R = H, 4-$NO_2C_6H_4$,

Scheme 9.

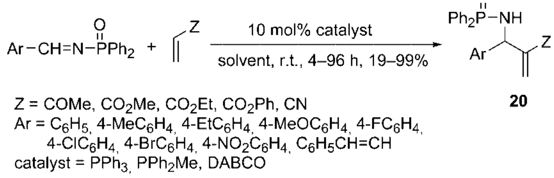
20. Reactions between phenyl acrylate and *N*-benzylidenediphenylphosphinamides yielded double aza-Baylis–Hillman adducts **21** along with cyclized adducts **22** (Scheme 13).[16]



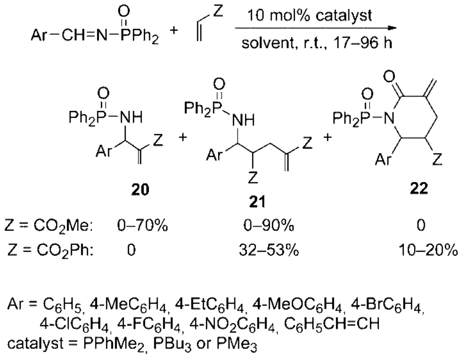
Scheme 10.



Scheme 11.

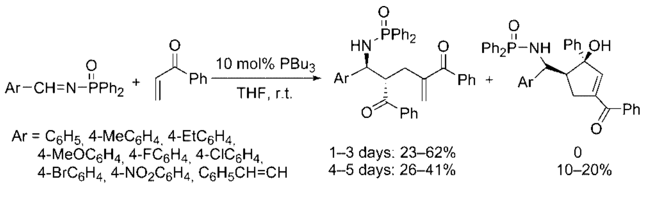


Scheme 12.



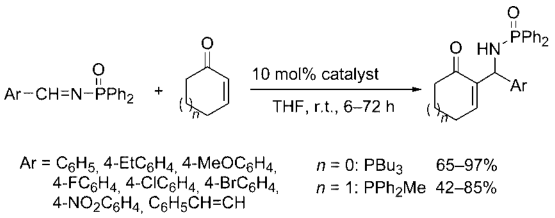
Scheme 13.

In the presence of PBu_3 as catalyst, the products of the reactions between phenyl vinyl ketone and N-benzylidenediphenylphosphinamides were dependent on the reaction times. Use of short reaction times resulted in the formation solely of double aza-Baylis–Hillman adducts, while use of longer reaction time resulted in mixtures of cyclized products and double aza-Baylis–Hillman adducts (Scheme 14).[16]



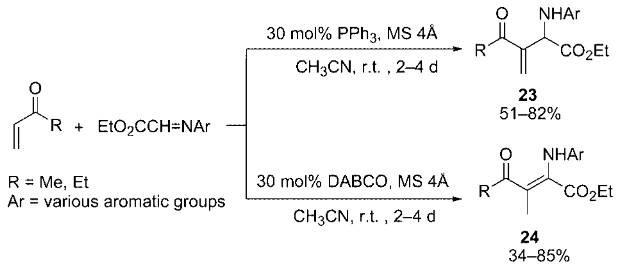
Scheme 14.

The reactions between cyclopent-2-en-1-one or cyclohex-2-en-1-one and N-benzylidenediphenylphosphinamides with PBu_3 or PPh_2Me, respectively, as catalysts gave aza-Baylis–Hillman adducts (Scheme 15).[16]



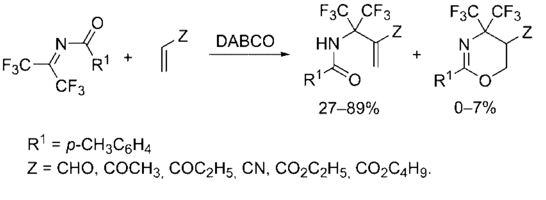
Scheme 15.

We recently reported aza-Baylis–Hillman reactions between ethyl (arylimino)acetate and methyl vinyl ketone or ethyl vinyl ketone.[17] In the presence of PPh_3 as catalyst, normal aza-Baylis–Hillman adducts were obtained, while use of DABCO as the catalyst resulted in double-bond-migrated products. Compound **23** could be converted into compound **24** upon treatment with catalytic amount of DABCO (Scheme 16).



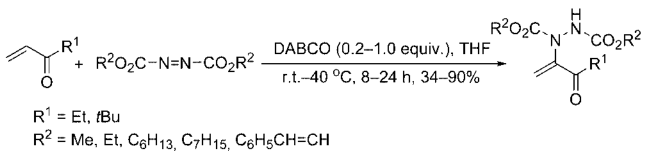
Scheme 16.

As well as aldehyde imines, Burger and Cyrener found that hexafluoroacetone N-benzoylimines were also suitable electrophiles for aza-Baylis–Hillman reactions with a variety of activated alkenes (Scheme 17).[18] Furthermore, they also found that use of CaH_2 as an additive could improve the yields of the reaction.[19]



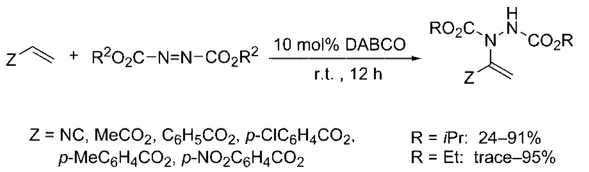
Scheme 17.

Azodicarboxylates were also suitable electrophiles for reactions with various activated alkenes. Kamimura et al. examined the reactions between alkyl vinyl ketones and azodicarboxylates[20] and found that they proceeded smoothly in the presence of DABCO as catalyst, giving the corresponding α-hydrazino-α,β-unsaturated ketones in moderate to high yields (Scheme 18).



Scheme 18.

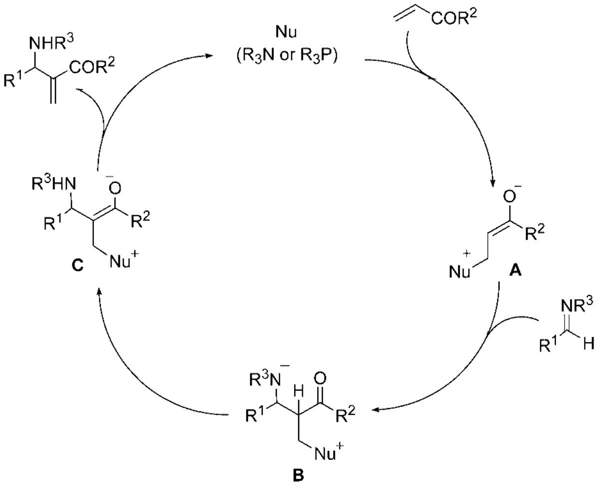
Later on, our group extended this methodology to reactions between azodicarboxylates and acrylates or acrylonitrile (Scheme 19).[21]



Scheme 19.

Mechanistic Study

The generally accepted mechanism of the aza-Baylis–Hillman reaction is shown in Scheme 20.[22]



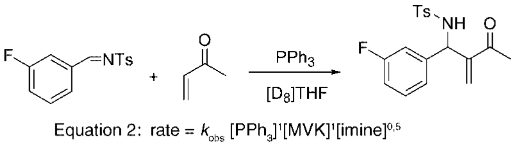
Scheme 20.

Jacobsen et al. monitored reactions between methyl acrylate and nosylimines in $CHCl_3$ in the presence of DABCO as catalyst by GC analysis.[23] The initial rates were found to follow Equation (1).

$$\text{rate} = \frac{a[\text{DABCO}][\text{Acrylate}][\text{Imine}]}{1 + b[\text{Imine}]} \tag{1}$$

A prominent primary kinetic isotope effect was observed (kH/kD = 3.81) on comparison of the initial reaction rate of methyl acrylate with that of separate reactions of α-deuteriomethyl acrylate, strongly suggesting that deprotonation of the α-H(D) (**B** to **C** in Scheme 20) was rate-limiting.

Leitner et al. monitored the aza-Baylis–Hillman reaction between methyl vinyl ketone and a fluorinated *N*-tosylated imine in the presence of PPh_3 in THF at room temperature by ^{19}F NMR spectroscopy (Scheme 21). The rate law derived by analysis of the initial rates as a function of concentration for the individual components is shown in Equation (2). The broken order of 0.5 in imine indicates that the rate-determining step (RDS) is partly influenced by proton transfer.[24]



Scheme 21.

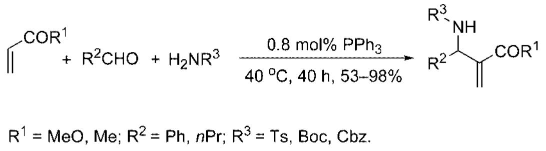
$$\text{rate} = k_{\text{obs}}[\text{PPh}_3]^1[\text{MVK}]^1[\text{Imine}]^{0.5} \tag{2}$$

A variety of Brønsted acidic additives with different pK_a values was examined, with 3,5-bis(CF_3)phenol – at a pK_a about 8 – corresponding to a 14-fold rate enhancement relative to the reaction without additive. Examination of the kinetics in the presence of phenol as a prototypical additive revealed that the rate law of the reaction changes in the presence of the Brønsted acid, showing first-order dependence in imine [Equation (3)], so the elimination step is no longer involved in the RDS, and the proton transfer is accelerated by the protic additive.[24]

$$\text{rate} = k_{\text{obs}}[\text{PPh}_3]^1[\text{MVK}]^1[\text{Imine}]^1 \tag{3}$$

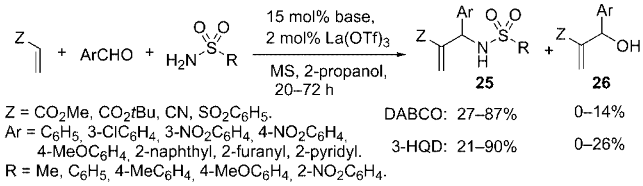
Multicomponent One-Pot Reactions

In 1989, Kahn et al. reported a three-component, one-pot procedure for this reaction.[25] However, β-substitution in the activated alkenes was not tolerated under the conditions (Scheme 22).



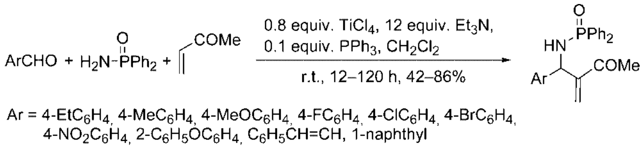
Scheme 22.

After that, multicomponent reactions were less explored. In 2001, Adolfsson and Balan described a three-component reaction with activated alkenes, aldehydes, and tosylamines.[26] In the presence of DABCO or 3-HQD as catalyst, together with $La(OTf)_3$ and molecular sieves, the aza adducts **25** were obtained in moderate to high yields, along with some alcohol adducts **26** (Scheme 23). Subsequently, they found that use of $Ti(OiPr)_4$ as the Lewis acid co-catalyst was superior to that of $La(OTf)_3$, giving better chemoselectivity in the aza adducts **3**.[27]



Scheme 23.

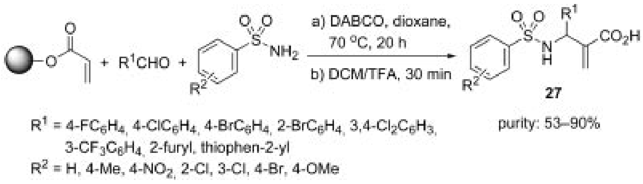
Furthermore, we found that one-pot, three-component reactions of arylaldehydes, diphenylphosphinamide, and methyl vinyl ketone could be achieved in the presence of $TiCl_4$, PPh_3, and Et_3N, giving the corresponding aza-Baylis–Hillman adducts in moderate to good yields (Scheme 24).[28]



Scheme 24.

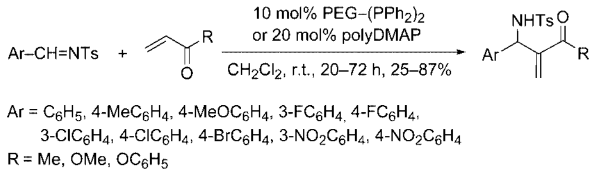
Polymer-Supported Reagents and Catalysts

In order to improve the efficiency of the catalysts and to simplify the workup procedures, polymer-supported reagents and catalysts have also been adopted in aza-Baylis–Hillman reactions. Jung and Richter reported a three-component reaction with polymer-bound acrylic acid, aldehydes, and sulfonamides in the presence of DABCO as catalyst.[29] After cleavage from the polymer support, the products **27** were obtained with high purities (Scheme 25).



Scheme 25.

The polymer-supported catalysts PEG-$(PPh_2)_2$ and polyDMAP were also adopted by us for reactions between *N*-tosyl imines and methyl vinyl ketone or acrylates.[30] The corresponding aza-Baylis–Hillman adducts were obtained in good yields and the catalysts could be easily recovered and reused (Scheme 26).



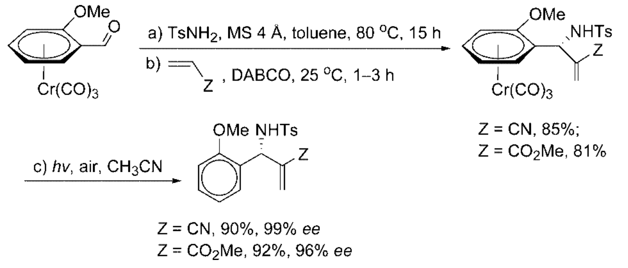
Scheme 26.

Later on, we and Toy et al. found that polystyrene-supported triphenylphosphane was an effective catalyst for the reactions between *N*-tosyl imines and methyl vinyl ketone.[31] The corresponding aza-Baylis–Hillman adducts were obtained in excellent yields and the catalysts could be reused. Subsequently, the non-phosphane-bearing styrene aromatic rings were functionalized with polar groups and a series of such catalysts were examined for their catalytic efficiency in a range of solvents.[32] It was observed that incorporation of 4-methoxystyrene into the polymer afforded the best support in terms of catalyst efficiency.

Asymmetric Aza-Baylis–Hillman Reactions

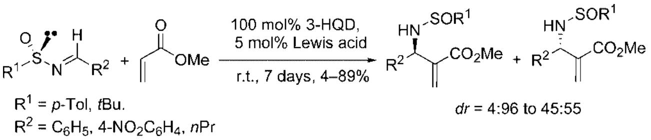
The early work in this area focused on the application of enantiopure electrophiles, while later on various chiral catalysts for the reaction were developed.

In 1994, Kündig et al. explored the reaction behavior of methyl acrylate and acrylonitrile in the presence of enantiopure planar chiral *o*-substituted $Cr(CO)_3$.[33] In the presence also of DABCO as catalyst, the corresponding aza-Baylis–Hillman adducts were obtained in good yields. Removal of the metal provided chiral amines in high yields and enantiomeric excesses (Scheme 27).



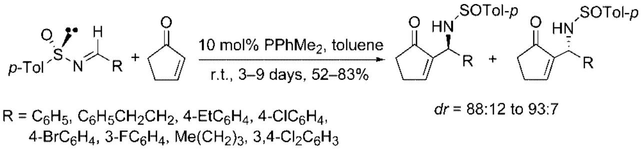
Scheme 27.

Later on, Aggarwal et al. used enantiopure *N*-sulfinimines in aza-Baylis–Hillman reactions with methyl acrylate in the presence of 3-HQD and Lewis acid. The desired adducts were obtained with good diastereoselectivities (Scheme 28).[34]



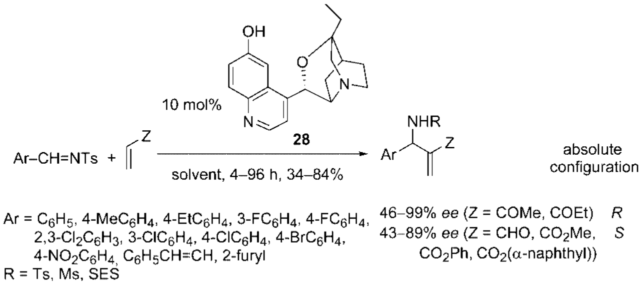
Scheme 28.

Subsequently, enantiopure *N*-sulfinimines were also adopted by us for reactions with cyclopent-2-en-1-one.[35] Good yields and diastereoselectivities of the aza-Baylis–Hillman adducts were achieved (Scheme 29).



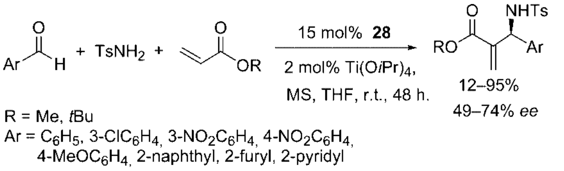
Scheme 29.

Great efforts to achieve catalytic asymmetric versions of the aza-Baylis–Hillman reactions have also been made. The chiral amine quinidine derivative **28** was used by us as a promoter for aza-Baylis–Hillman reactions between *N*-sulfonyl imines and various activated alkenes such as alkyl vinyl ketone, acrolein, and acrylates.[36,37] The corresponding adducts were obtained in moderate to good yields and with good to excellent enantiomeric excesses (Scheme 30).



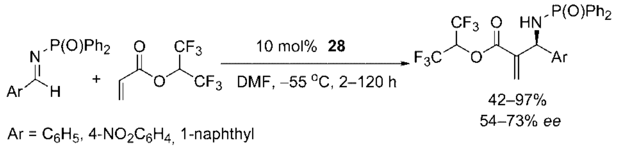
Scheme 30.

Adolfsson and Balan applied the same catalyst to the three-component reaction between acrylates, aldehydes, and tosylamines in the presence of Ti(O*i*Pr)$_4$ and molecular sieves as additives (Scheme 31).[38] Good yields and enantiomeric excess were also achieved.



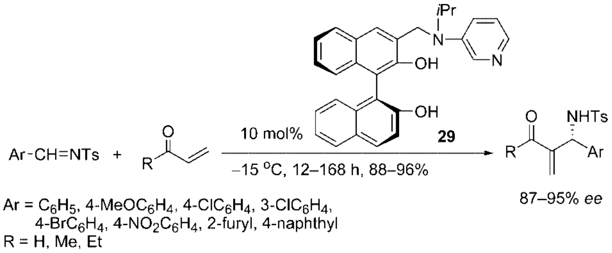
Scheme 31.

This catalyst was also adopted by Hatakeyama et al. in reactions between *N*-(arylmethylene)diphenylphosphinamides and hexafluoroisopropyl acrylate (HFIPA), giving the corresponding aza-Baylis–Hillman adducts in moderate to excellent yields and with good enantiomeric excesses (Scheme 32).[39]



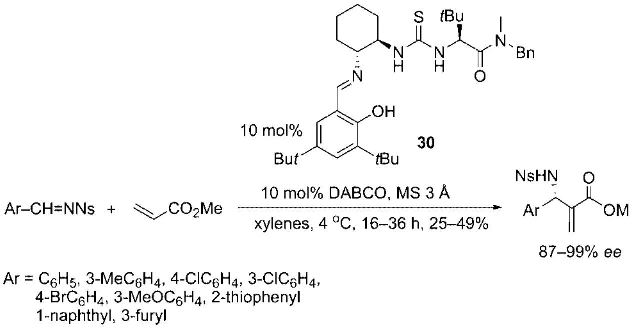
Scheme 32.

Recently, Sasai et al. reported a chiral asymmetric aza-Baylis–Hillman reaction of *N*-tosyl imines with acrolein and alkyl vinyl ketones catalyzed by the BINOL-derived amine **29**.[40] The corresponding aza-Baylis–Hillman adducts were obtained in good to excellent yields and with high enantiomeric excesses (Scheme 33). On replacement of the *i*Pr group in amine **29** with other substituents, the derived catalysts were less effective either in yield or enantioselectivity.[41]



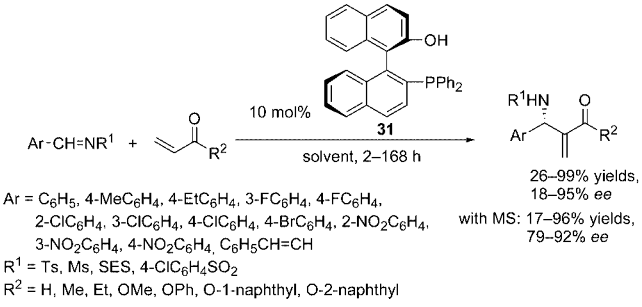
Scheme 33.

Jacobsen et al. have developed highly enantioselective catalytic aza-Baylis–Hillman reactions between nosylimines and methyl acrylate in the presence of chiral thiourea derivatives **30** and DABCO as co-catalyst (Scheme 34).[23]



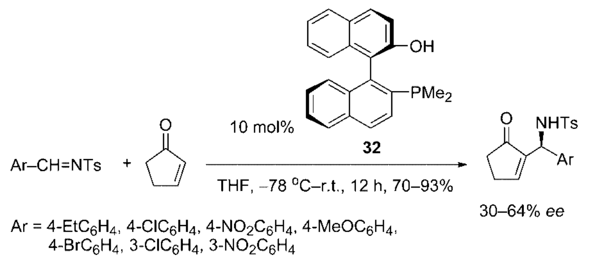
Scheme 34.

As well as chiral amines, we also found that the chiral phosphane **31** was a successful catalyst for asymmetric aza-Baylis–Hillman reactions between *N*-sulfonyl imines and acrolein, alkyl vinyl ketones, and acrylates (Scheme 35).[42,43]



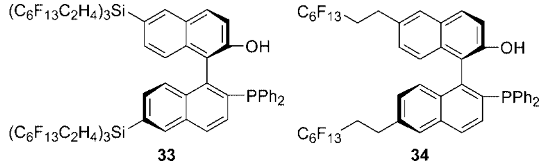
Scheme 35.

We subsequently synthesized a more nucleophilic chiral phosphane **32** and used it in aza-Baylis–Hillman reactions between *N*-sulfonyl imines and cyclohex-2-en-1-one or cyclopent-2-en-1-one.[44] The resulting adducts could be obtained in good yields and with moderate enantiomeric excesses (Scheme 36).



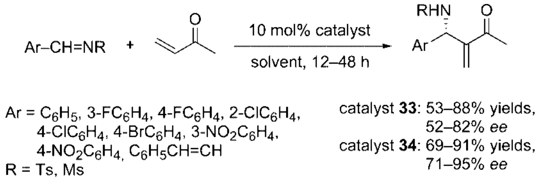
Scheme 36.

The structure of the catalyst **31** was then modified through the introduction of two perfluoroalkane chains onto the naphthalene framework (Figure 1); the corresponding adducts could be obtained in good yields and with good to excellent *ee* values.[45] Catalyst **34** was more effective in this reaction than the previously reported original chiral phosphane **1** (Scheme 37).



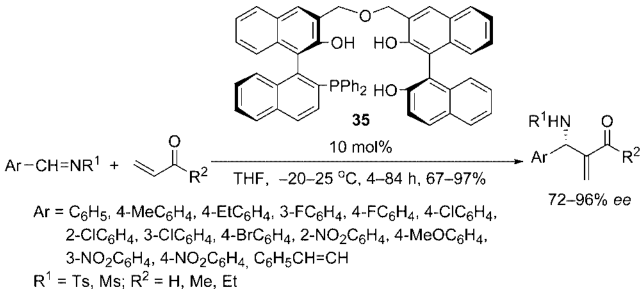
33 **34**

Figure 1. Chiral phosphane Lewis bases bearing perfluoroalkanes as "pony tails".



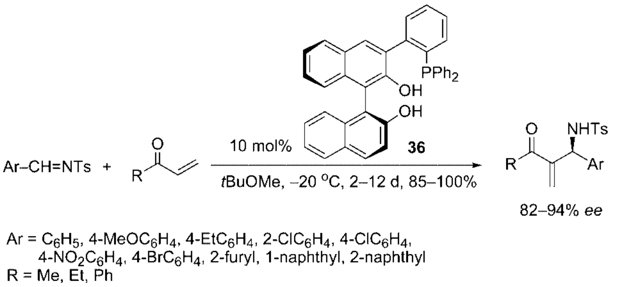
Scheme 37.

Later on, we modified catalyst **31** to incorporate a series of multiple phenol groups and it was found that catalyst **35** gave the best asymmetric induction.[46] The corresponding adducts could be obtained in >90% *ee*s and with good to excellent yields at –20 °C or room temperature (25 °C) in THF in the cases of most of the substrates with MVK, EVK, or acrolein as a Michael acceptor (Scheme 38).



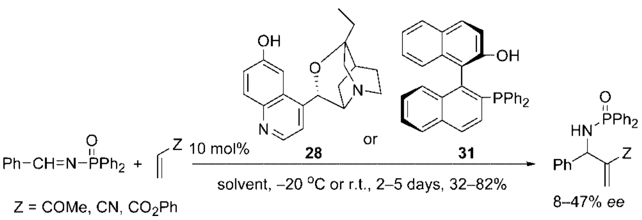
Scheme 38.

Sasai et al. also functionalized BINOL at the 3-position with a series of aryl phosphanes.[47] It was found that catalyst **36** was able to catalyze asymmetric aza-Baylis–Hillman reactions between *N*-tosyl imines and vinyl ketones effectively (Scheme 39).



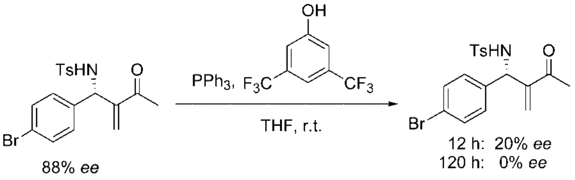
Scheme 39.

For reactions between *N*-(arylmethylene)diphenylphosphinamides and other ordinary activated alkenes such as methyl vinyl ketone, acrylonitrile, or phenyl acrylate, neither the chiral amine **28** nor the chiral phosphane **31** was able to provide a good enantiomeric excess (Scheme 40).[16]



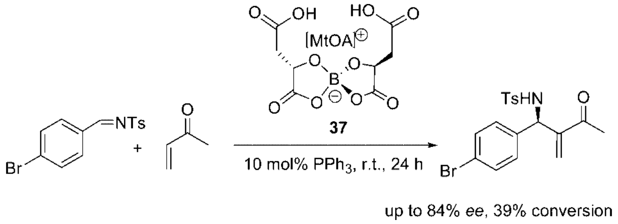
Scheme 40.

Leitner et al. found that triphenylphosphane, either alone or in combination with protonic additives, could cause racemization of the aza-Baylis–Hillman product through proton exchange at the stereogenic center, though the chiral catalyst **31** developed by our group did not induce any racemization on a similar timescale (Scheme 41).[24]



Scheme 41.

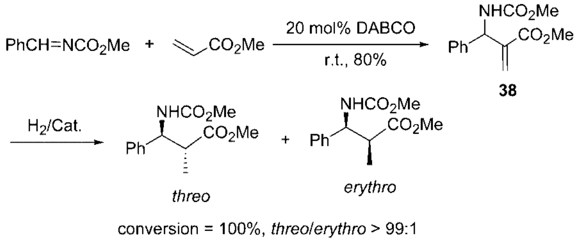
As well as chiral catalysts, chiral reaction media have also been found to display good asymmetric induction capabilities. Very recently, Leitner et al. performed reactions in the chiral ionic liquid methyltrioctylammonium dimalatoborate (**37**).[48] In the aza-Baylis–Hillman reaction between methyl vinyl ketone and *N*-(4-bromobenzylidene)-4-toluenesulfonamide, up to 84% *ee* and 39% conversion was observed (Scheme 42).



Scheme 42.

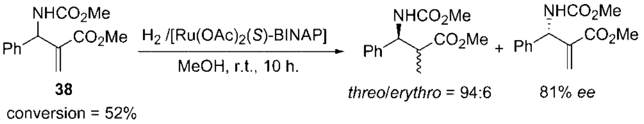
Applications of the Aza-Baylis–Hillman Adducts

In 1988, Yamamoto et al. reported diastereoselective hydrogenations of the adducts **38** derived from the aza-Baylis–Hillman reaction between methyl benzylidenecarbonate and methyl acrylate.[49] Excellent *anti* selectivity was observed. This was the first example of the transformation of a aza-Baylis–Hillman adduct (Scheme 43).



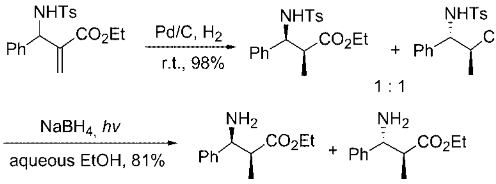
Scheme 43.

The same workers subsequently developed a kinetic resolution strategy for **38** through the use of chiral Rh^{I} or Ru^{II} catalysts.[50] One typical example is shown in Scheme 44.



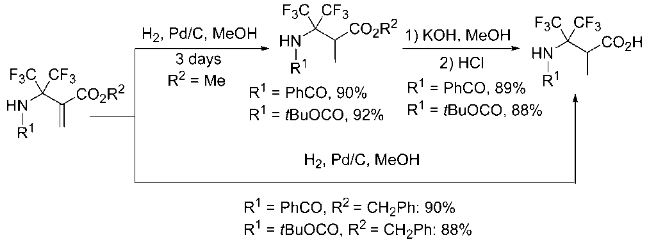
Scheme 44.

Later on, Perlmutter et al. described hydrogenations of the adducts derived from aza-Baylis–Hillman reactions between *N*-tosyl imines and ethyl acrylate and also investigated the direct photochemical reductive detosylation of the hydrogenated products.[51] One typical example is shown in Scheme 45.



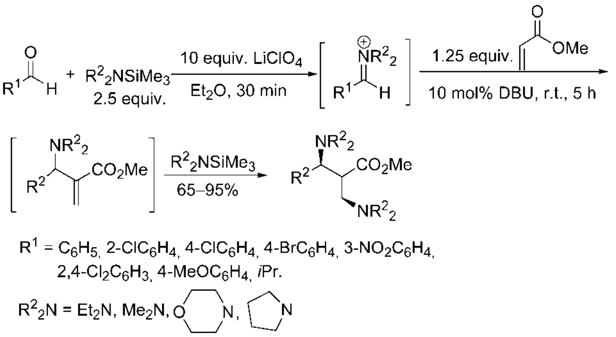
Scheme 45.

Burger et al. demonstrated a simple synthesis of partially fluorinated β-amino acids by hydrogenation (and subsequent hydrolysis if necessary) of the aza-Baylis–Hillman adducts derived from hexafluoroacetone *N*-benzoylimines and acrylates (Scheme 46).[19]



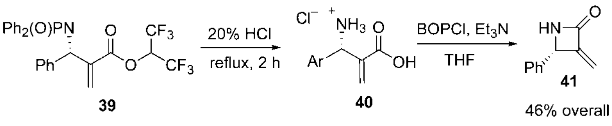
Scheme 46.

Saidi et al. used iminium salts prepared in situ as electrophiles for reactions with methyl acrylate in the presence of DBU as catalyst to give the corresponding aza-Baylis–Hillman adducts as intermediates, which were trapped by (trimethylsilyl)dialkylamines to give the diamines in good yields (Scheme 47).[52]



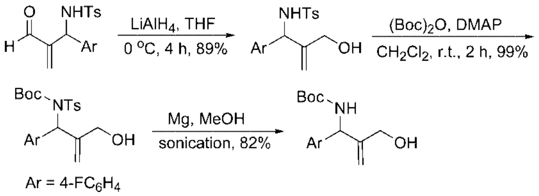
Scheme 47.

Hatakeyama et al. reported the conversion of the adduct **39** derived from *N*-(arylmethylene)diphenylphosphinamides and hexafluoroisopropyl acrylate into a β-lactam. The diphenylphosphinoyl group was cleaved upon acid hydrolysis to give the β-amino acid hydrochloride **40**, which was subsequently transformed into β-lactam **41** in the presence of BOPCl and triethylamine (Scheme 48).[39]



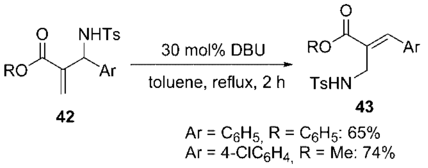
Scheme 48.

If tosyl groups in aza-Baylis–Hillman adducts could be easily removed, the synthetic utility of the amino adducts could be expanded. We reported that the tosyl group in the adduct derived from the aza-Baylis–Hillman reaction between *N*-tosyl imine and acrolein could be changed into the synthetically more useful Boc group in good yield (Scheme 49).[4]



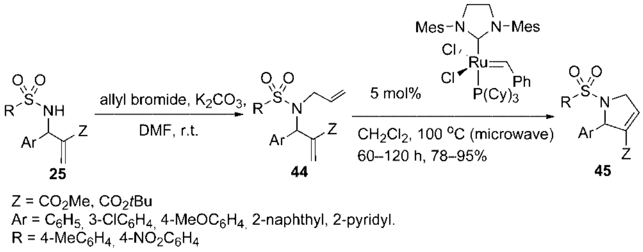
Scheme 49.

We also found that treatment of the adducts **42** derived from aza-Baylis–Hillman reactions between *N*-tosyl imines and phenyl acrylate could give rearranged products **43** (Scheme 50).[4]



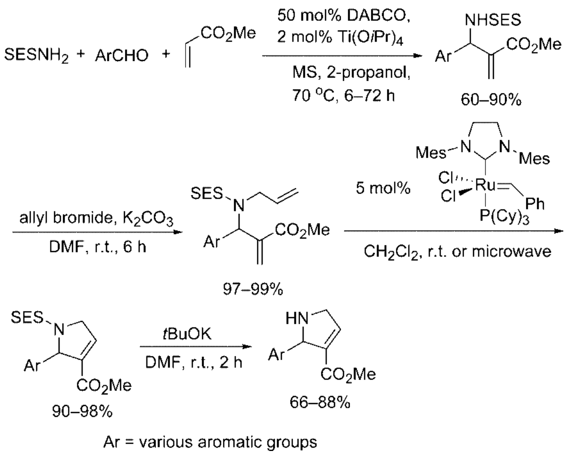
Scheme 50.

Adolfsson and Balan reported a rapid method for the formation of functionalized 2,5-dihydropyrroles **45** using ruthenium-catalyzed ring-closing metathesis under microwave irradiation.[53] The diene substrates **44** were efficiently prepared by allylation of the aza-Baylis–Hillman adducts **25** (Scheme 51).



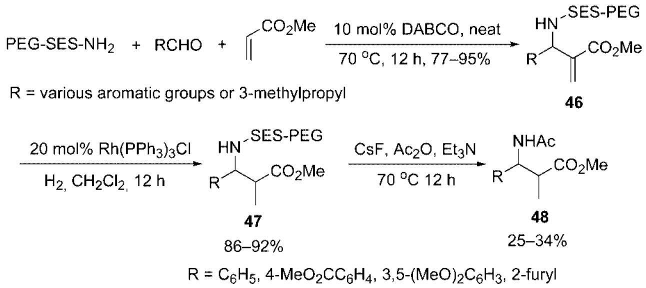
Scheme 51.

Later on, Lamaty et al. converted the tosyl group into a SES group by the above methodology.[54] The SES group was then cleaved under basic conditions (Scheme 52).



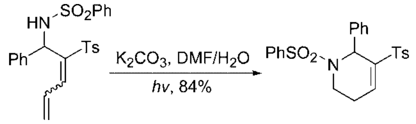
Scheme 52.

Lamaty et al. also developed three-component aza-Baylis–Hillman reactions between methyl acrylate, aldehydes, and PEG-SES amine in the presence of DABCO as catalyst, giving the adducts **46** in high yields.[55] Subsequent hydrogenation and desulfonylation converted the polymer-supported products **46** into β-amino esters **48** with high purities (Scheme 53).



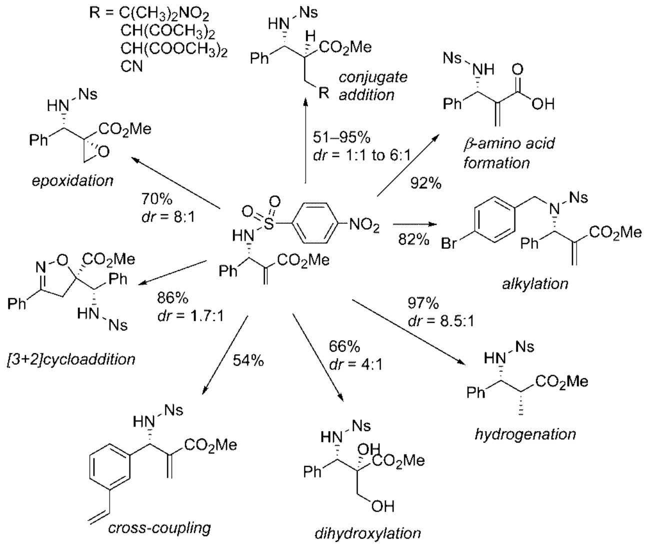
Scheme 53.

Back et al. reported that the adducts derived from aza-Baylis–Hillman reactions between imines and buta-1,3-diene sulfone could be cyclized to the corresponding functionalized piperidines in high yield in the presence of as catalyst of K_2CO_3 with UV light irradiation.[14] One representative example is shown in Scheme 54.



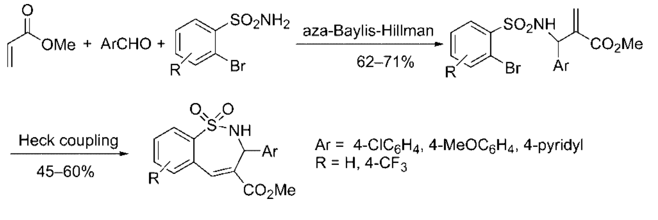
Scheme 54.

A variety of transformations of the aza-Baylis–Hillman adducts have more recently been demonstrated by Jacobsen et al. (Scheme 55).[23]

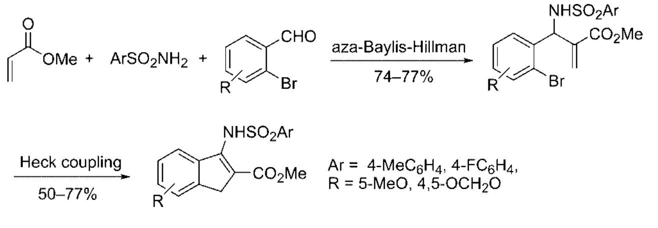


Scheme 55.

Vasudevan et al. synthesized a series of bicyclic scaffolds by intramolecular Heck coupling of aza-Baylis–Hillman adducts with an *ortho*-halo-substituted sulfonamide or aldehyde as the starting material (Scheme 56 and Scheme 57).[56]



Scheme 56.



Scheme 57.

Summary and Outlook

Although excellent progress has been made in the area of the aza-Baylis–Hillman reaction, many challenges and questions still remain. The detailed mechanism of the reaction is still undiscovered, the substrate scopes are still limited, and further synthetic applications of the corresponding adducts have yet to be fruitful. This field is developing at a rapid pace and surely further progress will be forthcoming.

Abbreviations

BINOL = 1,1′-bi-2-naphthol, Boc = *tert*-butyloxycarbonyl, BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride, Cbz = benzyloxycarbonyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = 4-(dimethylamino)pyridine, 3-HQD = 3-hydroxyquinuclidine, Ms = mesyl, MS = molecular sieves, MTOA = methyltrioctylammonium, Ns = *p*-nitrophenylsulfonyl, PEG = polyethylene glycol, SES = 2-(trimethylsilyl)ethylsulfonyl, TFA = trifluoroacetic acid, Ts = tosyl.

Acknowledgments

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