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aza-Baylis−Hillman Reaction

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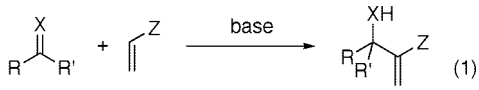
1. Introduction

The creation of carbon−carbon bonds remains an important challenge in organic synthesis. Numerous reactions for the formation of carbon−carbon bonds have been discovered and largely exploited. Recent progress in organic chemistry have clearly established that the development of a reaction is dependent on two main criteria: atom economy and selectivity (chemo-, regio-, stereo-).[1,2]

Recently, the Morita−Baylis−Hillman reaction[3,4] has appeared as a performant process for the formation of carbon−carbon bonds since it combines two important requirements (atom economy and functional group generation). Ignored for a long time after its discovery in 1968 by Morita[3] (phosphine-catalyzed reaction) and then in 1972 by Baylis and Hillman[4] (amine-catalyzed reaction), this reaction and its applications have received growing interest since the mid 1990s. The Morita−Baylis−Hillman reaction has been applied to a wide variety of substrates and allows the preparation of various families of molecules. Another reason for interest in the Baylis−Hillman reaction is the fact that it is possible to convert cheap starting materials, under the action of an appropriate catalyst, into highly functionalized compounds, which can be used for further transformations.

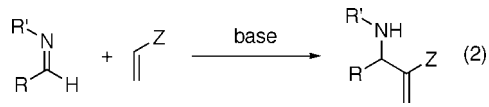
The Morita−Baylis−Hillman reaction can be described as the coupling between the α-position of an activated double bond and an sp^2 electrophilic carbon in the presence of an appropriate catalyst, generally a tertiary amine or phosphine, leading to the formation of a multifunctional molecule (eq 1).



(1)

X = O, NR''

The original process involved the use of an aldehyde. If this aldehyde is replaced by an imine, the reaction is called the *aza*-Baylis−Hillman reaction (eq 2). This reaction leads to α-methylene-β-amino derivatives and, in particular, to β-amino esters when an acrylate is used as a Michael acceptor.



(2)

If the Morita−Baylis−Hillman reaction and its applications in synthesis have already been extensively discussed in several reviews,[5−10] its *aza*-counterpart has been briefly summarized.[11,12] We will detail herein the *aza*-Baylis−Hillman reaction as well as its stereoselective versions. Thereafter, we will describe alternative access routes to these α-methylene-β-amino derivatives from Baylis−Hillman products or by other processes related to the *aza*-Baylis−Hillman reaction. Finally, we will present the use of these α-methylene-β-amino derivatives in synthesis.

Valérie Declerck (middle) was born in Nemours (France) in 1980. During her undergraduate education at the Institute of Technology in Le Mans, she trained with Professor J. Lebreton at the University of Nantes in 2000. She then moved to the University of Montpellier, where she obtained her DEA in 2003 and her Ph.D. degree in 2006 under the direction of Dr Frédéric Lamaty, working on the *aza*-Baylis−Hillman reaction and its applications in heterocyclic chemistry and also on solid-state peptide synthesis. In late 2006, she joined the group of Professor J. H. Rigby at Wayne State University (Detroit, MI) as a postdoctoral fellow to work on the total synthesis of Schelhammeridine and related alkaloids. In September 2008, she was appointed Assistant Professor at the University of Orsay (Paris-Sud 11) and joined the group of Professor D. J. Aitken at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO) where she works on the synthesis of constrained β-amino acids and their use as organocatalysts.

Jean Martinez (left) studied chemistry at the Ecole Nationale Supérieure de Chimie de Montpellier (France). After receiving his Ph.D. in 1972, he was awarded a permanent position at the CNRS. He completed his Thèse d'Etat in 1976 under the direction of Professor F. Winternitz, performed postdoctoral studies with Professor E. Bricas in Orsay (France) and at Case Western University (Ohio) with Professor M. Bodanszky. On his return to France, he pursued his research activities at the interface of chemistry and biology in the field of peptides. He became successively head of various research laboratories in Montpellier including the Laboratory of Chemistry and Pharmacology of Biologically Interesting Molecules and the Laboratory of Aminoacids, Peptides and Proteins (LAPP). In 1998, he left the CNRS and was appointed Professor of the Faculty of Sciences, and in 2001 he was appointed Professor of Medicinal Chemistry at the Faculty of Pharmacy. He is currently head of the Max Mousseron Institute for Biomolecules (IBMM). His research interests are peptide chemistry and pharmacology, stereoselective synthesis of amino acids, chemistry on polymeric supports, mass spectrometry, artificial proteins synthesis, computer-assisted peptide search, and green chemistry.

Frédéric Lamaty (right) graduated as a chemical engineer in 1988 from the Ecole Supérieure de Chimie Industrielle de Lyon (France). In 1992, he received his Ph.D. from Purdue University under the supervision of Professor E. Negishi in the field of Pd-catalyzed cyclizations. He then joined, as a Rhône-Poulenc postdoctoral fellow, the group of Professor M. Julia at the Ecole Normale Supérieure in Paris to work on the synthesis of Vitamin A. In 1994, he obtained a permanent position at the Centre National de la Recherche Scientifique (CNRS) in Montpellier and is currently working as Directeur de Recherche at the Max Mousseron Institute for Biomolecules (IBMM). His research topics include organic chemistry, catalysis, the synthesis of amino acids, heterocyclic chemistry, polymer-supported chemistry especially on PEG support, and green chemistry.

2. aza-Baylis−Hillman reaction

2.1. General Considerations

2.1.1. Mechanism

In contrast with the Morita−Baylis−Hillman reaction, only two mechanistic studies deal with the *aza*-version of this reaction.[13,14] In a similar manner to the Baylis−Hillman reaction, the *aza*-Baylis−Hillman reaction consists of a sequence of addition−elimination. In the case of the reaction

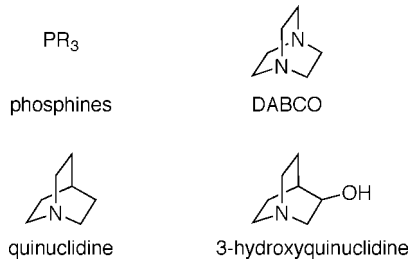
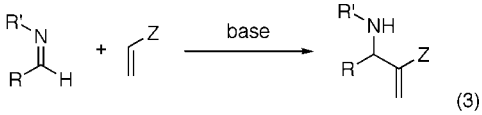


Figure 1.

of a tosylimine with a Michael acceptor, catalyzed by a tertiary amine or phosphine, the commonly adopted mechanism is presented in Scheme 1. The first step consists of a Michael-type nucleophilic addition of the catalyst on the activated double bond. The enolate thus formed is responsible for a nucleophilic attack on the imine. Finally, a proton transfer followed by an elimination of the catalyst furnishes the *aza*-Baylis−Hillman adduct. Addition of the catalyst to the Michael acceptor and attack of the resulting enolate to the imine are reversible, and the proton transfer constitutes the rate-determining step, but the reaction exhibits no autocatalysis. However, Leitner and co-workers have demonstrated that the use of a protic additive (Brønsted acid) leads to a substantial rate enhancement through acceleration of the elimination step.[13]

2.1.2. Substrate Diversity

The reaction is flexible toward the choice of starting materials (eq 3). As electrophiles, various activated aldimines like tosylimines,[15] nosylimines,[14] SES-imines,[15] and phosphinoylimines[16] can be used. The reaction can also be performed as a three-component reaction in which the aldehyde, the activated alkene, and tosylamide,[17,18] SES-NH_2,[19] or diphenylphosphinamide[20] are coupled in "one-pot". Furthermore, sulfinylimines[21,22] and azodicarboxylates[23,24] can be employed in the *aza*-Baylis−Hillman reaction.



(3)

R = Ar
R' = Ts, Ns, SES, SO_2Ph, PPh_2, CO_2Me
Z = CO_2R, COR, CN, CHO

The spectrum of Michael acceptors that can be used for this reaction is even broader.[25] Vinyl ketones, acrolein, acrylates, and cyclic enones as well as other β-substituted activated alkenes were reported as suitable Michael acceptors.[26,27] Also, activated allenes and alkynes are appropriate substrates.[28,29]

2.1.3. Catalysts

In a similar manner to the Baylis−Hillman reaction, the *aza*-Morita−Baylis−Hillman reaction can be mediated by nucleophilic Lewis bases (Figure 1), especially phosphines (*aza*-Morita−Baylis−Hillman reaction) and tertiary amines (*aza*-Baylis−Hillman reaction), mainly DABCO (1,4-diazabicyclo[2.2.2]octane), quinuclidine, and 3-hydroxyquinuclidine.

Various supported catalysts were also evaluated in the *aza*-Baylis−Hillman reaction, like supported equivalents of DMAP or supported phosphines,[30] with rather variable results. Modified quinuclidines, supported on ionic liquids, were also used with good results.[31]

Scheme 1

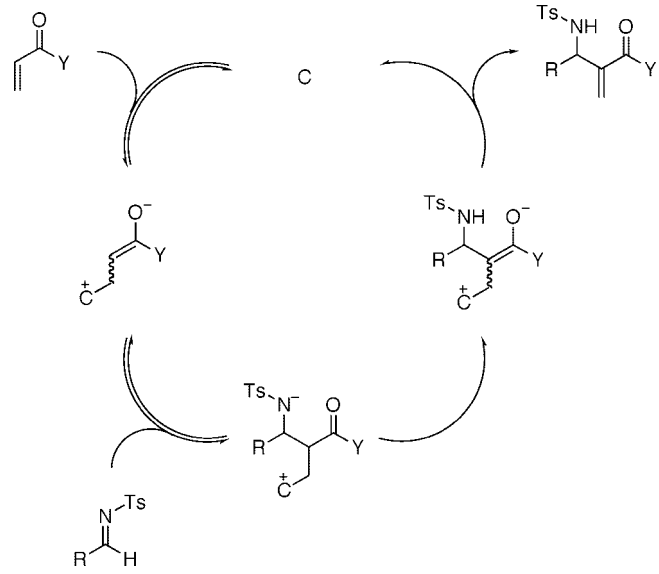
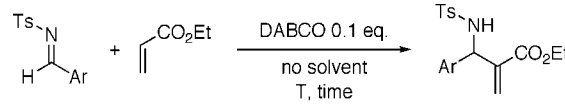


Table 1. First *aza*-Baylis−Hillman Reaction



Ar	*T* (°C)	time (h)	yield (%)
Ph	80	17	80
p-tolyl	80	17	73
p-anisyl	80	20	70
3-$O_2N-C_6H_4-$	50	48	53

2.1.4. Reaction Parameters: Solvents and Temperature

The *aza*-Baylis−Hillman reaction is generally slow. It is not rare to observe reaction times of several days, and its conversion rate is weak. In order to improve both reaction rate and yield, various conditions were employed according to the nature of the substrates used.

Although the dilution slowed down the Baylis−Hillman reaction, numerous solvents were used for this reaction. The solvent is mainly used to solubilize nonhomogeneous reaction mixtures and to promote the formation of zwitterionic species. For this reason, polar and/or protic solvents are the most appropriate ones (alcohols, acetonitrile, DMSO, DMF, and water).[32]

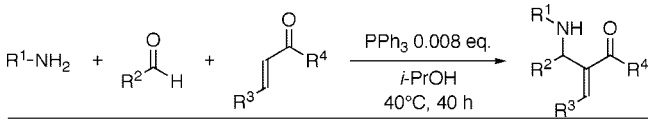
Most of the reactions were carried out at room temperature. Heating allows the acceleration of the reaction but can promote side reactions like olefin polymerization. The use of microwave heating[33] has already been described but was not the subject of a detailed study.

2.2. Use of Sulfonylimines

2.2.1. Early Results

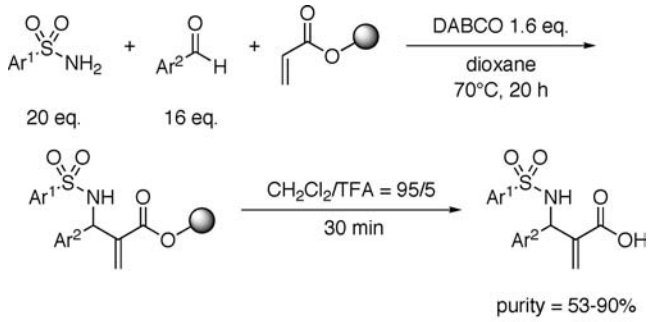
The sulfonylimines, in particular the tosylimines, are the most employed imines in the *aza*-Baylis−Hillman reaction. In 1984, Perlmutter and co-workers were the first to use tosylimines, derived from aromatic aldehydes, as electrophiles in the *aza*-Baylis−Hillman reaction.[34] Tosylimines reacted with ethyl acrylate in the presence of DABCO, upon heating, to provide the corresponding β-amino esters in good

Table 2. "One-Pot" *aza*-Morita−Baylis−Hillman Reaction



R^1	R^2	R^3	R^4	yield (%)
Ts	Ph	H	OMe	98
Ts	*n*-Pr	H	OMe	80
Z	Ph	H	OMe	53
Boc	Ph	H	Me	50
Ts	Ph	Me	OMe	0

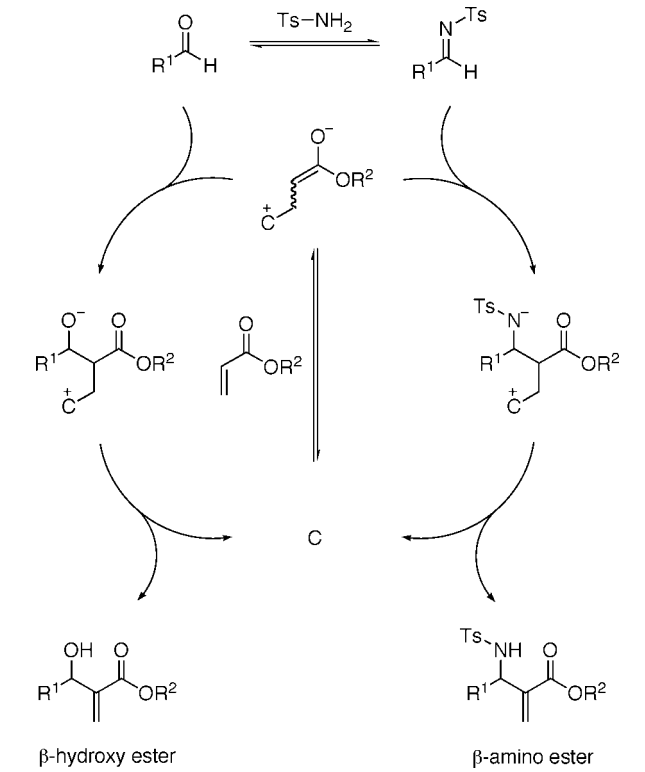
Scheme 2



Ar^1 = Ph, *p*-Tolyl, *p*-Anisyl, 2-Cl-C_6H_4-, 3-Cl-C_6H_4-, 4-Br-C_6H_4-, 4-O_2N-C_6H_4-, 5-Me_2N-α-Np-

Ar^2 = 4-F-C_6H_4-, 4-Cl-C_6H_4-, 2-Br-C_6H_4-, 4-Br-C_6H_4-, 3,4-Cl_2-C_6H_3-, 3-F_3C-C_6H_4-, 2-Furyl, 2-Thienyl

Scheme 3



yields (Table 1). As in the case of the traditional Baylis−Hillman reaction, β-substituted systems did not react.

Despite these good results, this reaction remained unused until 1988, when the group of Yamamoto described the synthesis of methyl 2-methoxycarbonylaminobenzylacrylate in order to study its diastereoselective hydrogenation.[35,36] Thereafter, in 1989, Bertenshaw and co-workers described the first three-component *aza*-Morita−Baylis−Hillman reaction during which the sulfonylimine is generated in situ from tosylamine and an aldehyde (aromatic or aliphatic) (Table 2).[37] The reaction was catalyzed by triphenylphosphine and was carried out in isopropanol. The reaction also took place with carbamates, although the formed imine was less electrophilic. Again, β-substituted systems did not react.

2.2.2. Use of Supported Acrylates

In 1998, Jung and co-workers described a "one-pot" reaction with an acrylate supported on a 2-chlorotrityl polystyrene type resin.[38] While varying the aldehyde and the sulfonamide, the reaction allowed the preparation of a library of α-methylene-β-amino acids, after cleavage of the support. The support allowed the use of excess reagents, which, in addition to heating, contributed to accelerate the reaction. The reaction provided a mixture of β-amino acid and β-hydroxy acid in undetermined proportions:

2.2.3. "One-Pot" Reaction

While the two-component reaction is still being developed,[25,39] the group of Adolfsson improved the three-component *aza*-Baylis−Hillman reaction.[17,18] In order to carry out enantioselective reactions thereafter, this group has tried to develop reaction conditions, at room temperature, that were compatible with a wide variety of aldehydes and activated olefins. This was difficult since, at room temperature, the imine formation is not favored and there is a competition between the attack of the enolate on the starting aldehyde and on the imine, which are in equilibrium in the reaction medium (Scheme 3). The reaction thus provides a mixture of β-amino ester resulting from the attack of the enolate on the imine and of the corresponding β-hydroxy ester resulting from a direct attack of the enolate on the aldehyde.

The main challenge thus consisted of increasing the chemoselectivity of the reaction and its kinetics. It was thus necessary to push the equilibrium toward the formation of the imine and to increase its reactivity with the enolate. To reach this goal, the use of molecular sieves allowed the trapping of the water resulting from the formation of the imine, and the use of a Lewis acid selective of the imine[40] allows its activation toward nucleophilic attack. The following results were obtained:

(i) It is necessary to use a larger quantity of base than Lewis acid, since the base coordinates itself partly to the Lewis acid and, thus, cannot play its catalytic role. This is in accordance with the results obtained by Aggarwal[41] for the two-component reaction.

(ii) The most effective bases are DABCO and 3-HQD. The latter allows the reduction of the reaction time by two, but it is slightly less selective.

(iii) Few differences could be observed among the different Lewis acids that were used, but $Sc(OTf)_3$, $Yb(OTf)_3$, and $Ti(O\textit{i}\text{-}Pr)_4$ are more efficient and more selective. The $Cu(OTf)_2$, which is very selective, gives, however, lower yields. Among these four Lewis acids, only $Ti(O\textit{i}\text{-}Pr)_4$ and $Cu(OTf)_2$ can displace the equilibrium toward the formation of the imine. Finally, a kinetic study has shown that the most suitable Lewis acid was $Ti(O\textit{i}\text{-}Pr)_4$.

The method thus developed allows the preparation of α-methylene-β-amino esters in short times, with good yields

and very good chemoselectivity (Scheme 4). The reaction has also been applied to other activated olefins with a very good selectivity, but lower yields.

Lamaty and co-workers have carried out the first *aza*-Baylis−Hillman reaction using an amine anchored on a polymeric support.[33,42] A sulfonamide derived from the [2-(trimethylsilyl)ethane]sulfonyl (SES),[43] supported on a soluble polymer, the poly(ethylene glycol), reacted with an aldehyde and an acrylate to provide supported β-amino esters. The SES group was used simultaneously as protecting group of the amine, activating group of the imine, and linker to the polymeric support (Scheme 5). The reaction has several advantages. First of all, the reaction is carried out in solvent-free conditions. Moreover, it is possible to use excesses of reagents to reduce the reaction time without any consequences on the purification step, since the only product being anchored on the support at the end of the reaction is the β-amino ester, in contrast to the work of Jung and co-workers in which a supported acrylate was used (section 2.2.2).[38]

This reaction was then adapted to SES−NH_2 to produce various SES-protected unsaturated β-amino esters.[19] A large variety of aromatic aldehydes were used to give the corresponding β-amino esters in good yields (Scheme 6).

2.2.4. aza-Baylis−Hillman Reaction of Acrylamides

Recently, Guo and co-workers have reported the use of acrylamide and *N*-arylacrylamide in the *aza*-Baylis−Hillman reaction with tosylimines (Table 3).[44] The reaction proceeded in good yields, but reaction times were considerably longer with *N*-arylacrylamides than with acrylamide.

2.2.5. aza-Baylis−Hillman Reaction of Activated Conjugated Dienes

Back and co-workers have investigated the vinylogous *aza*-Baylis−Hillman reaction of sulfonylimines with activated conjugated dienes.[45−47] The reaction is efficient with conjugated dienes activated by sulfones, esters, and cyano and keto groups, and it produces the β-amino compounds as a mixture of *E* and *Z* isomers. Except in the case of the cyano group, which gives mainly the *Z* isomer with a high selectivity, the *E* product is favored, especially in the case of the acyl group.

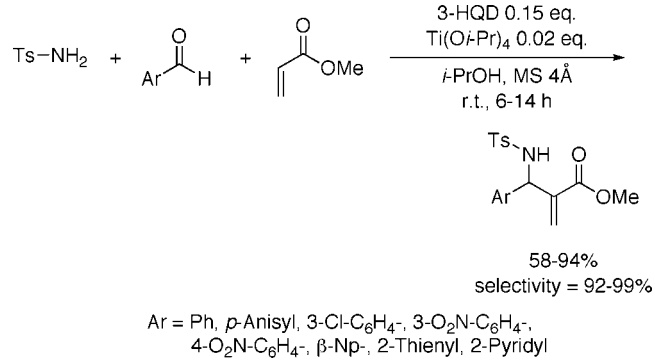
2.2.6. Use of Supported Catalysts

With the development of supported chemistry and supported reagents, various supported catalysts were tested in the *aza*-Baylis−Hillman reaction, allowing easier purification.

2.2.6.1. Supported Equivalents of DMAP. In 2003, Shi and co-workers used a supported equivalent of DMAP to carry out the reaction of methyl vinyl ketone with aromatic tosylimines.[30] Unfortunately, the yields obtained are rather modest, as is generally the case with DMAP (Scheme 7). Attempts to reuse the catalyst showed a reduced catalytic activity for the second cycle.

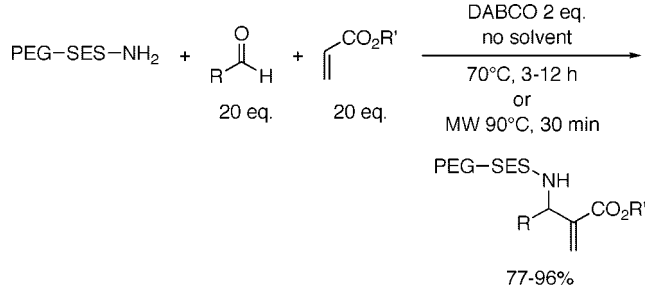
2.2.6.2. Supported Phosphines. The same group has also used a PEG-supported equivalent of methyldiphenylphosphine.[30] Although the catalyst gave good results for phenyl acrylate, yields were modest with methyl vinyl ketone and methyl acrylate (Tables 4 and 5), and the catalyst was completely inefficient for acrylonitrile.

Scheme 4

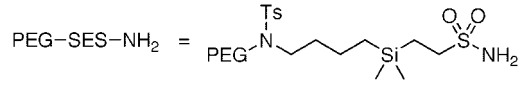


Ar = Ph, *p*-Anisyl, 3-Cl-C_6H_4-, 3-O_2N-C_6H_4-, 4-O_2N-C_6H_4-, β-Np-, 2-Thienyl, 2-Pyridyl

Scheme 5

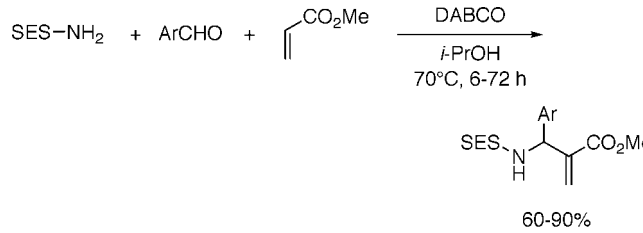


PEG−OH = $H(OCH_2CH_2)_nOH$ with an average MW = 3400



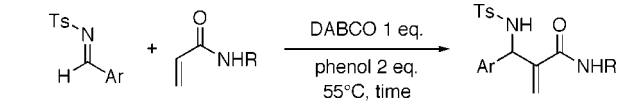
R = Ph, *m*-Tolyl, *p*-Tolyl, 3,5-$(MeO)_2$-C_6H_3-, 3-HO-C_6H_4-, 2-(AllylO)-C_6H_4-, 4-Cl-C_6H_4-, 2-I-C_6H_4-, 4-MeO_2C-C_6H_4-, 4-O_2N-C_6H_4-, 2-Furyl, 2-Thienyl, 3-Pyridyl, *i*-Bu
R' = Me, Et

Scheme 6



Ar = Ph, *m*-Tolyl, 3,5-Me_2-C_6H_3-, 3,5-$(MeO)_2$-C_6H_3-, 2,3-(OCH_2O)-C_6H_3-, 4-TMS-CC-C_6H_4-, 3-F-C_6H_4-, 4-Cl-C_6H_4-, 2-Br-C_6H_4-, 2-I-C_6H_4-, 4-MeO_2C-C_6H_4-, 4-O_2N-C_6H_4-, β-Np, 2-Furyl

Table 3. *aza*-Baylis−Hillman Reaction of Acrylamide Derivatives



R	time	yield (%)
4-O_2N−C_6H_4−	4−5 d	61−67
H	2−6 h	71−93

With the same objective, this group has described the synthesis and the use of JandaJel-supported equivalents of triphenylphosphine.[48,49] The results are better than those previously obtained but still strongly depend on the nature of the substrate (Table 6).

Scheme 7

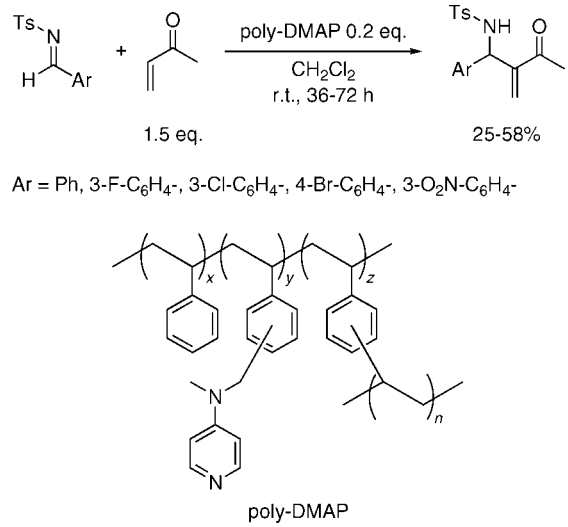
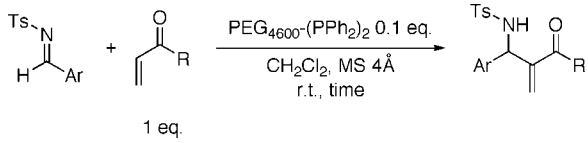


Table 4. Vinylogous *aza*-Baylis−Hillman Reaction of Activated Conjugated Dienes

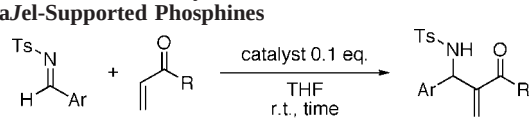
EWG	additive	time	selectivity *E*/*Z*	yield (%)
Ts		4−6 h	50/50 → 70/30	31−86
CO_2Me	MeOH (traces)	1−3 d	75/25 → 80/20	61−91
COMe	MeOH (traces)	6−12 h	>95/5	47−80
COPh	MeOH (traces)	6−12 h	60/40 → 70/30	30−88
CN	MeOH 6 equiv	7−12 h	>5/95	18−78

Table 5. *aza*-Morita−Baylis−Hillman Reaction with a PEG-Supported Phosphine



R	time (h)	yield (%)
Me	20−72	25−77
OMe	72	20
CN	72	0
OPh	36	50−87

Table 6. *aza*-Morita−Baylis−Hillman Reaction with JandaJel-Supported Phosphines



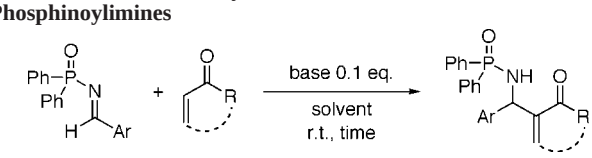
R, *x* equiv	catalyst, loading	time (h)	yield (%)
Me, 1.5 equiv	*JJ*−PPh_3, 1.5 mmol·g^{-1}	10−30	63−99
H, 2 equiv	*JJ*−OMe−PPh_3, 1.0 mmol·g^{-1}	3	36−75
OPh, 1.2 equiv	*JJ*−OMe−PPh_3, 1.0 mmol·g^{-1}	36	45−81

2.3. Other Imines

2.3.1. Sulfinylimines

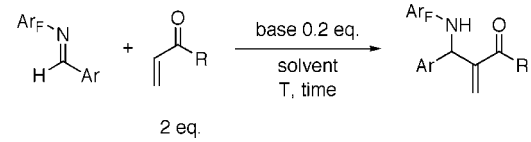
Sulfinylimines are very good chiral intermediates that have been used in the asymmetric synthesis of amines, α-amino acids, and *β*-amino acids. The *N*-sulfinyl groups possess, in addition to its capacity to induce a selectivity, the advantage of being eliminated under relatively mild conditions compared to their *N*-sulfonyl counterparts. Although their synthesis requires several steps,[50] a fast "one-pot" synthesis of chiral *N*-*p*-toluenesulfinylimines starting from a commercial chiral sulfinate was developed.[51]

Table 7. *aza*-Morita−Baylis−Hillman Reaction with Phosphinoylimines



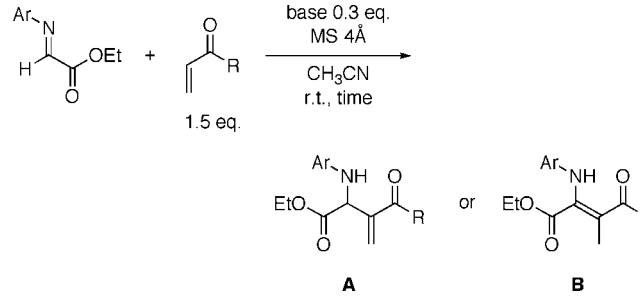
R	base	solvent	time (h)	yields (%)
Me	PPh_3	CH_3CN	24−48	77−99
OMe	PPh_2Me	CH_2Cl_2	4−96	40−92
CN	DABCO	CH_3CN	24−72	27−86
OPh	PPh_3	CH_3CN	24−72	19−66
Et	PPh_3	THF	24−72	38−59
Ph	PBu_3	THF	24−92	20−62
$(CH_2)_2$	PBu_3	THF	6−24	60−97
$(CH_2)_3$	$PPhMe_2$	THF	24−72	42−85

Table 8. *aza*-Morita−Baylis−Hillman Reaction with Fluorinated Imines



R	Ar_F	base	solvent	*T* (°C)	time (h)	yield (%)
Me	C_6F_5	PPh_3	THF	r.t.−40	12−96	20−80
	4-Cl-C_6F_4	PPh_3	THF	40−60	24−72	30−90
OMe	C_6F_5	3-HQD	DMF	r.t.	24−160	37−98
	4-Cl-C_6F_4	3-HQD	DMF	r.t.	24−160	20−77
CN	C_6F_5	DABCO	DMF	r.t.−60	68−160	54−72
	4-Cl-C_6F_4	DABCO	DMF	r.t.−60	48−120	35−69

Table 9. *aza*-Morita−Baylis−Hillman Reaction of Arylimino Acetates



R	base	time (d)	product	yield (%)
Me	PPh_3	2−4	A	52−81
Me	DABCO	2−4	B	34−85
Et	PPh_3	3−4	A	51−82
Et	DABCO	4	B	50−72

In 2002, Aggarwal and co-workers have used *N*-sulfinylimines as chiral electrophiles in the *aza*-Baylis−Hillman reaction[22] since they can undergo various nucleophilic additions with good diastereoselectivity, and the nature of the sulfinylimine can modulate the imine reactivity. Unfortunately, the results obtained in the *aza*-Baylis−Hillman reaction were relatively disappointing. It required long reaction time (up to 7 days). The use of a Lewis acid proved to be essential to obtain acceptable yields, but the diastereoselectivity was not as good as the one generally obtained in other reactions with sulfinylimines (eq 4). *tert*-Butanesulfinylimines proved to be poor substrates, even in the presence of a Lewis acid, while they generally exhibited a better diastereoselectivity due to the presence of the *t*-butanesulfinyl group, which ensured a better discrimination of the two faces of the imine.

Scheme 8

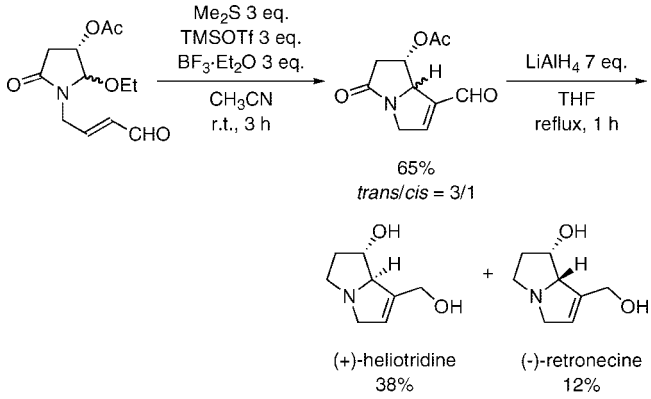
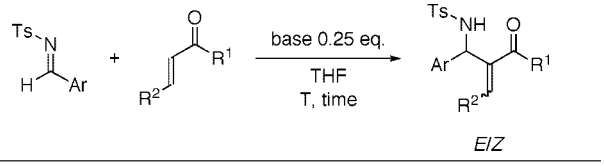
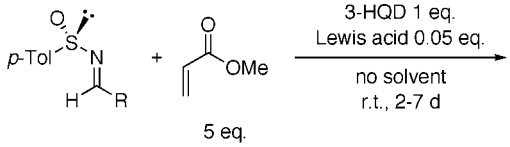
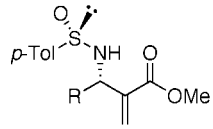


Table 10. *aza*-Morita−Baylis−Hillman Reaction with *β*-Substituted Michael Acceptors



R^1	R^2	base	*T* (°C)	time (h)	yield (%)	selectivity *E*/*Z*
H	Me	PPh_2Me	r.t.	15−72	40−80	>99/1
Ph	Me	$PPhMe_2$	r.t.	3−9	63−68	80/20 → 84/16
Ph	Me	PPh_2Me	r.t.	36−72	45−86	44/56 → 100/0
Me	Me	$PPhMe_2$	r.t.	0.6−3	12−40	81/19 → 91/9
H	Pr	$PPhMe_2$	0	2−12	30−53	87/13 → 93/7
Ovinyl	Me	$PPhMe_2$	r.t.	3−48	44−79	73/27 → 92/8
OPh	Me	$PPhMe_2$	r.t.	4−216	44−80	70/30 → 90/10
O-α Np	Me	$PPhMe_2$	r.t.	2−120	60−91	73/27 → 94/6
SPh	Me	$PPhMe_2$	r.t.	2−144	50−63	100/0
OPh	vinyl	DABCO	r.t.	6−120	32−75	69/31 → 89/11





(4)

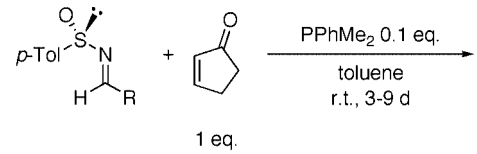
R = Ph, *p*-Anisyl, 4-O_2N-C_6H_4-, *n*-Pr
Lewis acid: $Sc(OTf)_3$, $Yb(OTf)_3$, $In(OTf)_3$

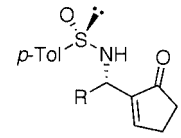
S_S,S
45-89%
de = 54-88%

Shi and co-workers then used these *N*-*p*-toluenesulfinylimines in the dimethylphenylphosphine-catalyzed reaction with cyclopentenone.[21] Reaction times were still long, but the yields were better than those obtained with methyl acrylate. Diastereoselectivity was not very good but was more homogeneous than in the precedent case (eq 5).

2.3.2. Phosphinoylimines, Thiophosphinoylimines, and Thiophosphorylimines

Phosphinoylimines were also used by the Shi group.[16,52] The imine was prepared starting from a phosphonic amide and an aldehyde, where the phosphinoyl group could be easily deprotected in acidic medium.[53] The results obtained were quite good, in particular for methyl vinyl ketone and cyclopentenone, with conditions close to those used for tosylimines (Table 7). On the other hand, for other Michael acceptors, results varied according to the starting phosphinoylimine.



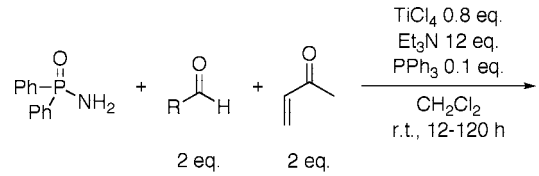


(5)

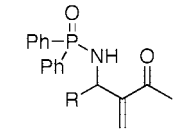
R = Ph, 4-Et-C_6H_4-, 3-F-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 3,4-Cl_2-C_6H_3-, Ph-$(CH_2)_2$-, *n*-Bu

S_S,S
52-83%
de = 76-86%

Thereafter, a "one-pot" version of this reaction was developed, but the results obtained were modest and the reaction times were long (eq 6).[20]

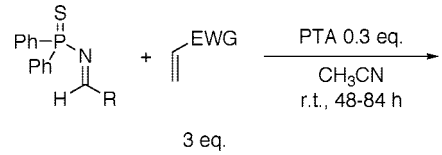


(6)

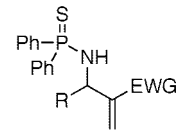


R = Ph, *p*-Tolyl, 4-Et-C_6H_4-, *p*-Anisyl, 3-PhO-C_6H_4-, 4-F-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 4-O_2N-C_6H_4-, α-Np, Cinnamyl

40-86%

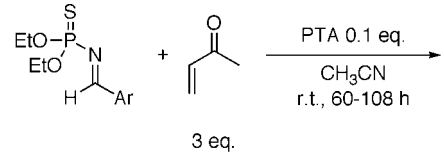


(7)

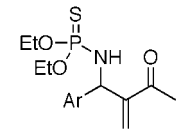


EWG = CO_2Me, COMe
R = Ph, *p*-Tolyl, *o*-Anisyl, 3-F-C_6H_4-, 2-Cl-C_6H_4-, 4-Br-C_6H_4-, 3-F_3C-C_6H_4-, 4-O_2N-C_6H_4-, Cinnamyl

33-92%



(8)

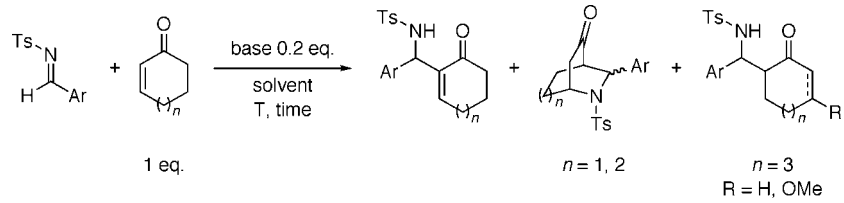


Ar = Ph, *p*-Tolyl, *m*-Anisyl, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 4-O_2N-C_6H_4-, 2-Furyl

67-92%

He and co-workers described the *aza*-Morita−Baylis−Hillman reaction of thiophosphinoylimines with methyl vinyl ketone and methyl acrylate (eq 7) and thiophosphorylimines with methyl vinyl ketone (eq 8) catalyzed by PTA (1,3,5-triaza-7-phosphaadamantane).[39,54] The reaction was carried out under mild conditions to give the adducts in fair-to-excellent yields.

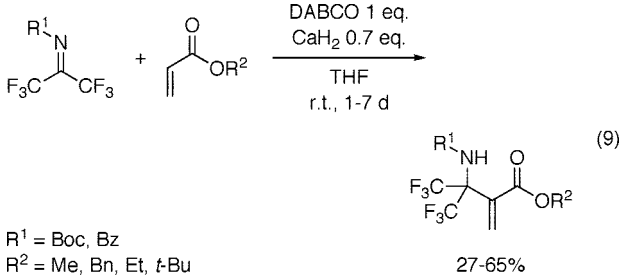
Table 11. *aza*-Morita−Baylis−Hillman Reaction with Cyclic Enones



n	base	solvent	*T* (°C)	time (h)	yield (%)	side products (%)
0	DMAP	MeOH	40	24	54−82	0
0	PBu_3	THF	40	5−6	70−99	0
1	PBu_3 or DBU	MeOH	40	3−26	15−40	28−48
1	DMAP	MeOH	40	24−36	30−65	0
2	PBu_3	THF	r.t.	5−6	0	0
2	DMAP or DBU	THF	r.t.	48	traces−27	14−22
3	PBu_3	THF	r.t.	48	0	30−49
3	DMAP	MeOH	r.t.	48	0	44−51

2.3.3. Fluorinated Imines

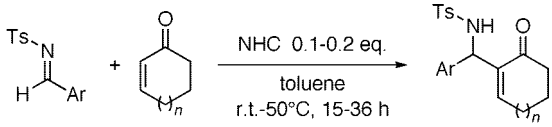
Burger and co-workers used fluorinated imines, prepared from the hexafluoroacetone, for the synthesis of fluorinated β-amino esters.[55] Under the traditional conditions of the *aza*-Baylis−Hillman reaction, the conversion was low. On the other hand, the addition of calcium hydride improved the reaction rate, but yields remained modest (eq 9).



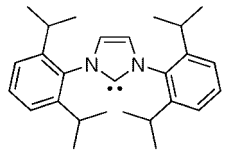
(9)

The Zhu group also used fluorinated imines carrying an electron-withdrawing polyfluoroaryl group on the nitrogen atom that activates the imine (Table 8).[56,57] Yields obtained were generally good, except for imines prepared from aldehydes substituted by electron-releasing groups. The results obtained were similar regardless of the Michael acceptor, except for acrolein, which provided only polymerization products.

Scheme 9



Ar = Ph, *p*-Tolyl, *o*-Anisyl, *m*-Anisyl, *p*-Anisyl, 4-F-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-, 4-O_2N-C_6H_4-, 2-Furyl



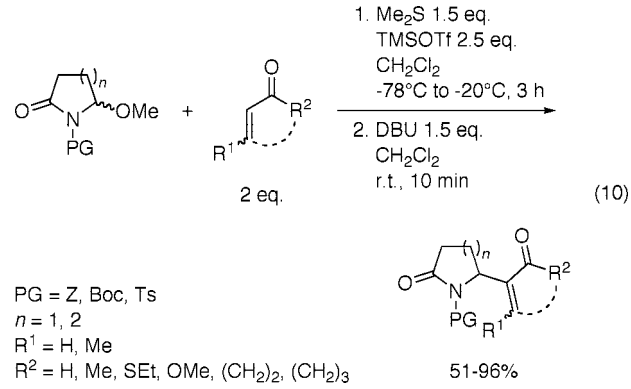
NHC

2.3.4. Arylimino Acetates

The group of Shi has reported the use of ethyl (arylimino)acetate as an electrophile in the *aza*-Morita−Baylis−Hillman reaction with vinyl ketones in the presence of triphenylphosphine (Table 9).[58] Interestingly, using DABCO as a base allowed the migration of the double bond to the internal position.

2.3.5. In Situ Generated Iminium Ions

Recently, Aggarwal and co-workers developed the *aza*-Baylis−Hillman reaction of in situ generated iminium ions (eq 10).[59,60] The reaction is catalyzed by Me_2S in the presence of a Lewis acid. This reaction was then applied to the synthesis of the necine base (+)-heliotridine starting from an appropriately substituted pyrrolidone (Scheme 8).[60]

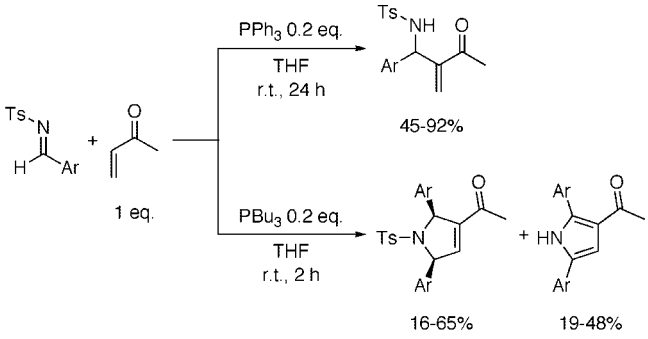


(10)

2.4. β-Substituted Michael Acceptors

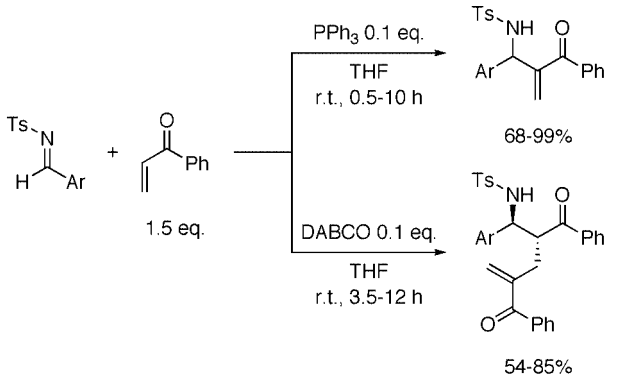
β-Substituted Michael acceptors are generally less reactive under Baylis−Hillman reaction conditions. The group of Shi has recently shown that the use of bases like PPh_2Me or $PPhMe_2$ instead of the commonly used base (DABCO, 3-HQD, QD, or PPh_3) allows the reaction of these β-substituted Michael acceptors (Table 10).[26,27] Yields are

Scheme 10



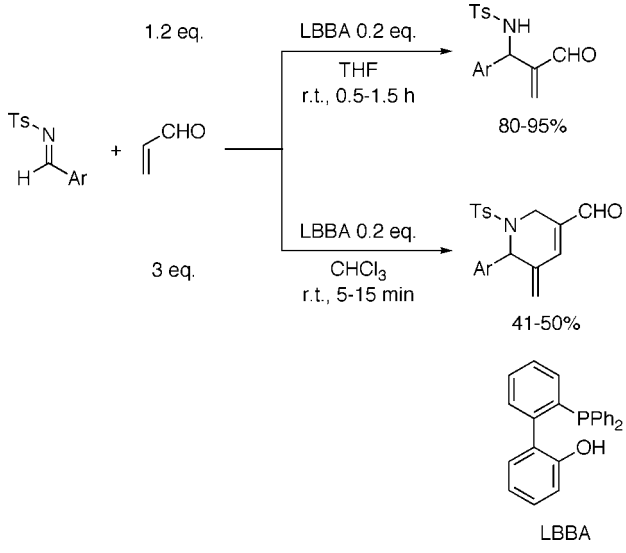
Ar = Ph, *p*-Tolyl, *p*-Anisyl, 3-F-C_6H_4-, 4-F-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 2,3-Cl_2-C_6H_3-, 4-O_2N-C_6H_4-, 2-Furyl, Cinnamyl

Scheme 11



Ar = Ph, *m*-Tolyl, *p*-Tolyl, 4-Et-C_6H_4-, *p*-Anisyl, 3-F-C_6H_4-, 4-F-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 2,3-Cl_2-C_6H_3-, α-Np

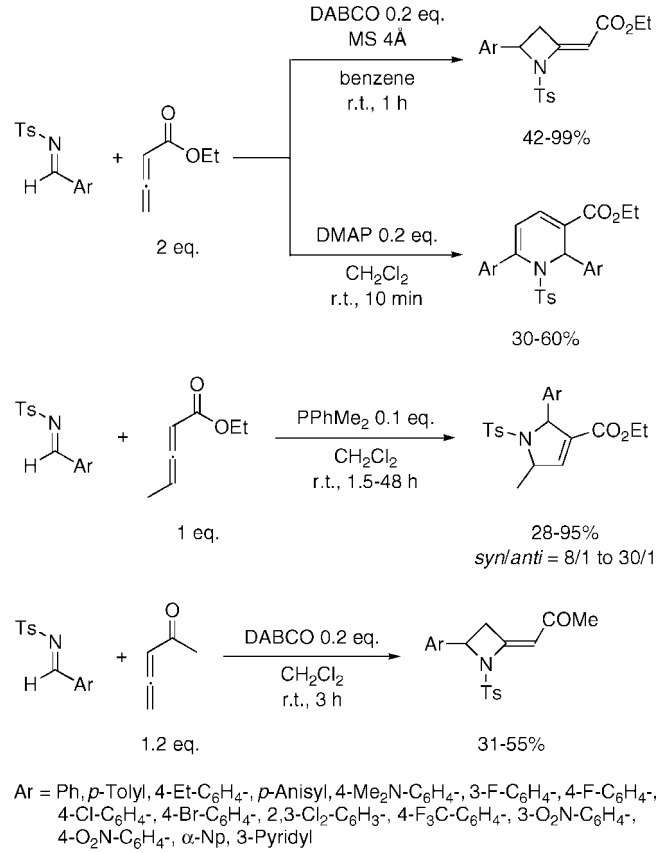
Scheme 12



Ar = *p*-Tolyl, 4-F-C_6H_4-, 2-Cl-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 2,4-Cl_2-C_6H_3-, 3-O_2N-C_6H_4-, 4-O_2N-C_6H_4-, Cinnamyl

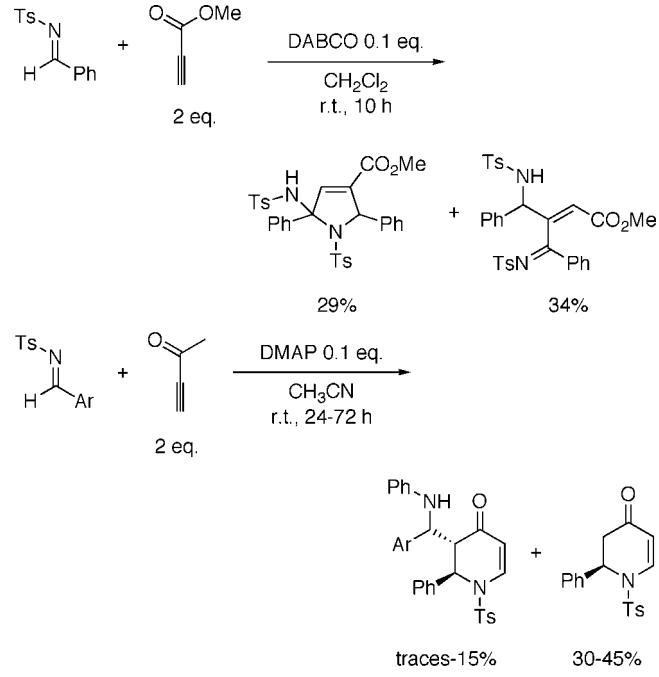
acceptable, and the *E*/*Z* selectivity varies according to the nature of the Michael acceptor used, with phenyl thiobut-2-enoate giving exclusively the *E* product and crotonaldehyde being also very selective. In the other cases, the selectivity varies with the nature of the aryl group, with the reaction providing mainly the *E* product.

Scheme 13



Ar = Ph, *p*-Tolyl, 4-Et-C_6H_4-, *p*-Anisyl, 4-Me_2N-C_6H_4-, 3-F-C_6H_4-, 4-F-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 2,3-Cl_2-C_6H_3-, 4-F_3C-C_6H_4-, 3-O_2N-C_6H_4-, 4-O_2N-C_6H_4-, α-Np, 3-Pyridyl

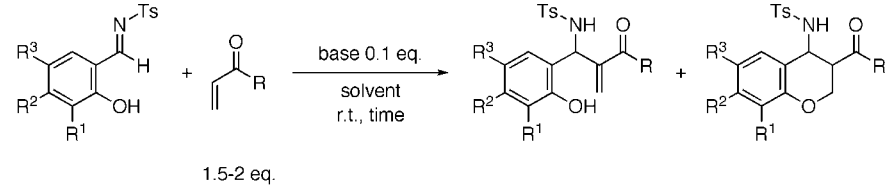
Scheme 14



Ar = Ph, *p*-Tolyl, 4-Et-C_6H_4-, *p*-Anisyl, 4-F-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-

Recently, Namboothiri and co-workers have prepared α-aminoalkylated conjugated nitroalkenes exhibiting an anticancer activity, by *aza*-Baylis−Hillman reaction of conjugated nitroalkenes with tosylimines catalyzed by imidazole in the presence of LiCl (eq 11).[61] Unfortunately, in most of the cases, yields are poor and reaction times are very long.

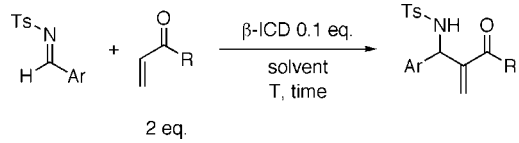
Table 12. *aza*-Baylis−Hillman Reaction of Salicyl *N*-Tosylimines



R^1 = H, OMe, Cl R^2 = H, OMe R^3 = H, OMe, Br, Cl, Me R = Me, Et, Ph

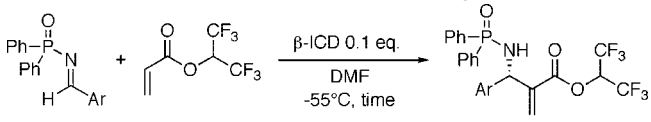
base	solvent	time (h)	β-aminocarbonyl compound (%)	chromane (%) (*trans*/*cis*)
DABCO	THF	12−48	0−84	0−99 (67:33 → 80:20)
DABCO	toluene	12−48	0−56	11−99 (67:33 → 80:20)
PPh_3	THF	18−240	0−48	41−82 (60:40 → 86:14)

Table 13. Enantioselective *aza*-Baylis−Hillman Reaction



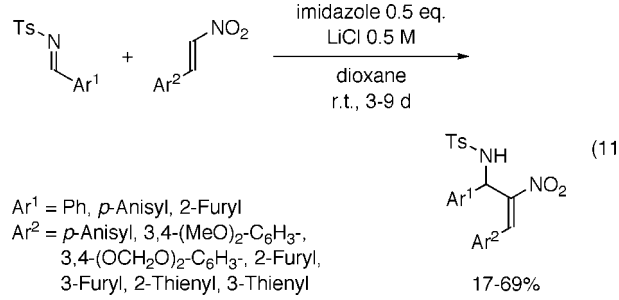
R	solvent	*T* (°C)	time (h)	yield (%)	ee (%)	configuration
Me	CH_3CN/DMF = 1/1	−30	24−36	54−80	46−99	*R*
Et	CH_3CN/DMF = 1/1	−30	22−41	46−54	82−94	*R*
H	THF	−25	4−20	55−72	83−89	*S*
OMe	CH_2Cl_2	0	32−72	58−87	70−83	*S*
OPh	CH_3CN	−20	8−20	67−84	67−82	*S*
OαNp	CH_3CN	0	12	67−85	78−80	*S*
CN	CH_2Cl_2 or THF	0	12	34−40	40−68	*S*

Table 14. *aza*-Baylis−Hillman Reaction using *β*-Isocupredine



				after recrystallization	
Ar	time (h)	yield (%)	ee (%)	yield (%)	ee (%)
Ph	120	90	67	55	95
p-anisyl	96	42	73	32	96
4-O_2N−C_6H_4−	2	97	54	57	93
α-Np	48	79	72	40	100
β-Np	120	16	[a]	[b]	

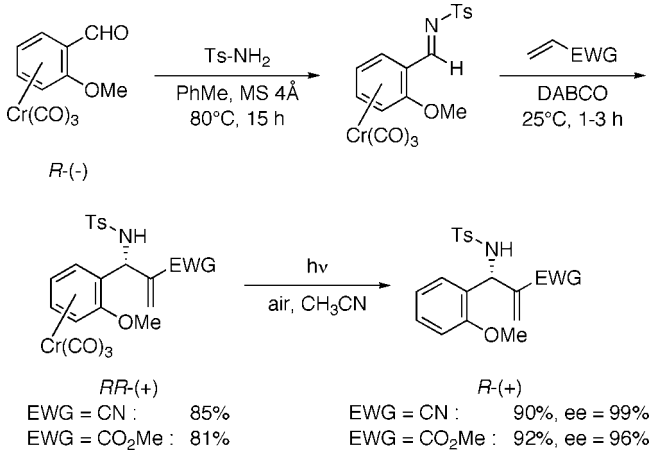
[a] Not determined. [b] Not performed.



2.5. Formation of Unexpected Products

In a number of cases, the *aza*-Baylis−Hillman reaction furnished unexpected products. The formation of these products depends on the nature of the Michael acceptor and on the conditions employed. In some cases, it is even possible to direct or control the reaction conditions to form the classical or unexpected products.

Scheme 15



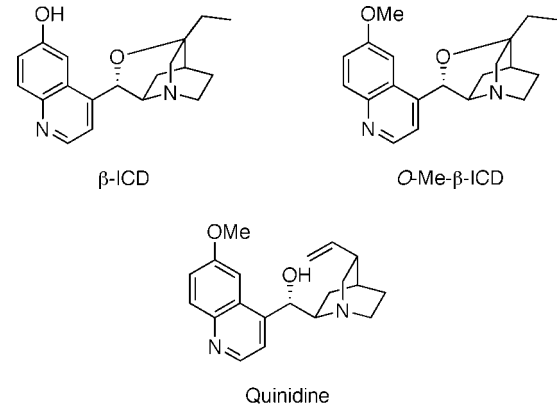


Figure 2.

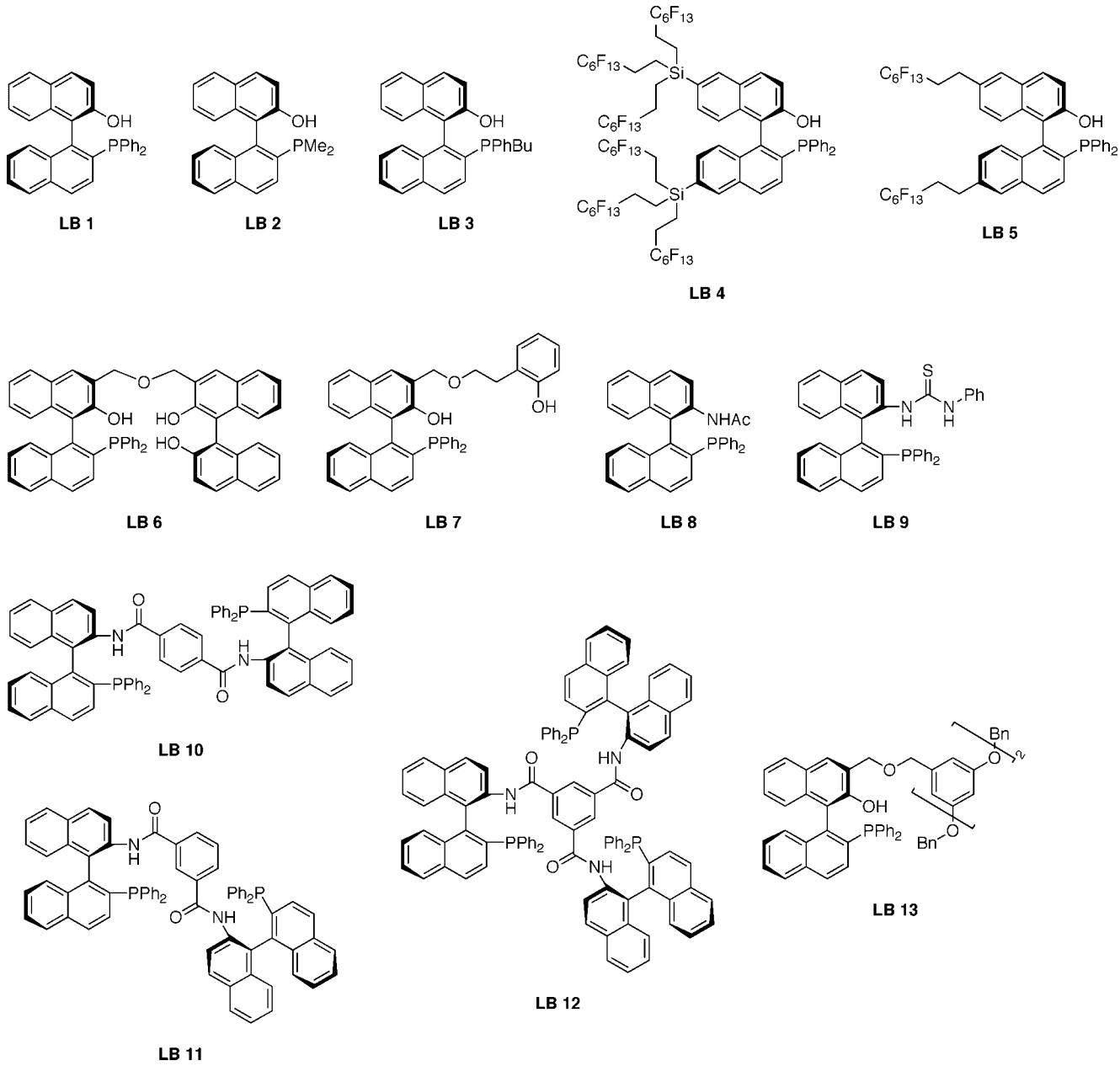


Figure 3.

2.5.1. Reaction with Cyclic Enones

In 2002, Shi and co-workers have studied the reaction of cyclic enones with tosylimines in the presence of different bases (Table 11).[62,63] With cyclopentenone, only the classical *aza*-Baylis−Hillman adduct was obtained independently of the base used. As the size of the cycle increased, side products appeared. In the case of cyclohexenone, the use of PBu_3 or DBU gave a mixture of *aza*-Baylis−Hillman adduct and products resulting from an aldol condensation followed by an intramolecular Michael addition. On the other hand, the use of DMAP gave only the *aza*-Baylis−Hillman product. The use of PBu_3 with cycloheptenone did not give any reaction, while DMAP or DBU provided mixtures of *aza*-Baylis−Hillman adduct and products resulting from an aldol condensation followed by an intramolecular cyclization. In the case of cyclooctenone, the *aza*-Baylis−Hillman adduct could not be formed but other secondary products were obtained. The use of PBu_3 provided the aldol condensation product, whereas the use of DMAP in methanol gave a product resulting from an addition on the imine followed by Michael addition of methanol on the double bond.

All these side reactions could be avoided by the use of a new class of catalyst. Ye and co-workers have recently demonstrated that *N*-heterocyclic carbenes (NHCs) are very efficient catalysts for the *aza*-Baylis−Hillman reaction.[64] Under the influence of NHCs, cyclopentenone and cyclohexenone react with tosylimines to give the *aza*-Baylis−Hillman adducts in high yields (Scheme 9).

2.5.2. Reaction with Vinyl Ketones

Shi and co-workers also studied the reaction of methyl vinyl ketone with tosylimines.[65] In this reaction, the use of triphenylphosphine furnishes the classical *aza*-Morita−Baylis−Hillman products in good yields, whereas the use of tributylphosphine gives a mixture of pyrroline and a pyrrole resulting from the dehydrodesulfinylation of the tosyl group of the pyrroline in the basic reaction medium (Scheme

Scheme 16

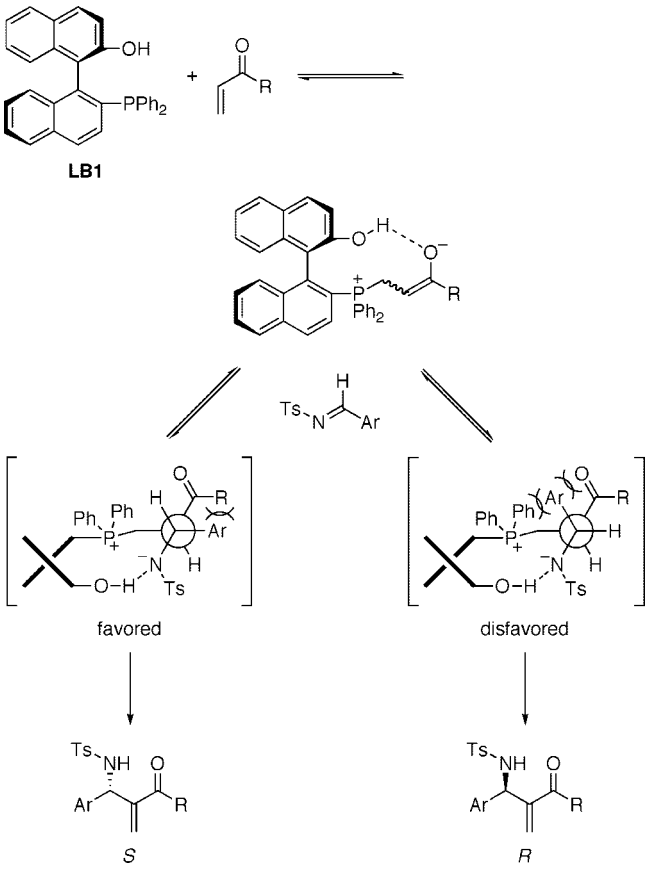
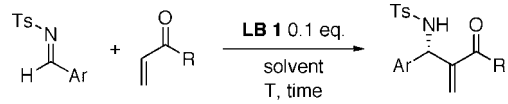
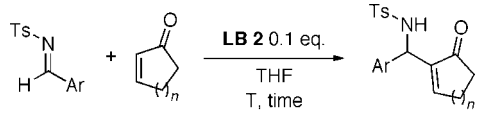


Table 15. Enantioselective *aza*-Morita−Baylis−Hillman Reaction



R	solvent	*T* (°C)	sieves 4Å	time (h)	yield (%)	ee (%)
Me	THF	−30	with	24−36	82−96	79−92
Et	THF	−20	with	48−168	17−85	80−92
OMe	CH_2Cl_2	r.t.		76	67	18
OPh	CH_2Cl_2	reflux		12	60−97	52−77
Oα-Np	CH_2Cl_2	r.t.		12	49	58
Oβ-Np	CH_2Cl_2	r.t.		12	57	53
H	THF	r.t.		4−12	74−99	76−86

Table 16. Enantioselective *aza*-Morita−Baylis−Hillman Reaction



n	*T* (°C)	time (h)	yield (%)	ee (%)
1	−78 → r.t.	12	70−93	30−55
2	r.t.	24	66−90	14−23

10). Although PTA allows an efficient reaction of thiophosphorylimines with methyl vinyl ketone, the PTA-catalyzed reaction with tosylimines produces a mixture of the *aza*-Baylis−Hillman adduct and the pyrroline previously described.[39]

In the case of the phenyl vinyl ketone, it is also possible to control the selectivity of the reaction.[66] Thus, the use of triphenylphosphine gives only the *aza*-Baylis−Hillman adduct. On the other hand, the use of DABCO leads to the formation of a product resulting from an aldol condensation of the phenyl vinyl ketone dimer with the tosylimine; the double adduct thus obtained is exclusively in an *anti*-configuration (Scheme 11). The same type of reaction occurs with imines bearing a polyfluoroaryl group on the nitrogen atom.[57]

2.5.3. Reaction with Acrolein

The use of acrolein in the *aza*-Baylis−Hillman reaction gives generally poor results because of its propensity to polymerize under the basic reaction conditions. However, using LBBA, a bifunctional phosphine organocatalyst, Huang and co-workers were able to cleanly couple acrolein with tosylimines.[67] When THF was used as the solvent, the *aza*-Baylis−Hillman adduct was obtained in high yield, but switching to $CHCl_3$ resulted in the formation of a tetrahydropyridine via a domino *aza*-Morita−Baylis−Hillman reaction/Michael addition/aldol condensation/dehydration sequence (Scheme 12). It can be assumed that the oxygen atom of THF could stabilize the anionic reaction intermediate by hydrogen bonding. Such stabilization is not possible with $CHCl_3$, and the anion reacts with a second molecule of acrolein.

2.5.4. Reaction with Activated Allenes and Alkynes

The *aza*-Baylis−Hillman reaction of tosylimines with activated allenes and alkynes was studied by the group of Shi.[28,29] These particular Michael acceptors lead to the formation of unusual products.

Thus, the reaction of tosylimines with ethyl buta-2,3-dienoate in the presence of DABCO leads to the formation of azetidines, whereas in the presence of DMAP, it produces 1,2-dihydropyridines.[28,29] When ethyl penta-2,3-dienoate is used in the presence of $PPhMe_2$, pyrrolines are formed in various yields.[29] These pyrrolines are formed via a [2+3]-cycloaddition induced by a carbanion, which was previously formed by addition of the phosphine on the allene. The use of penta-3,4-dien-2-one in the presence of DABCO provides azetidines with modest yields, along with many unidentified products (Scheme 13).[28,29]

The reaction of tosylimines with methyl propiolate in the presence of DABCO provides a mixture of pyrroline and γ-amino ester.[29] On the other hand, the reaction with but-3-yn-2-one in the presence of DMAP provides a mixture of 2,3-dihydropyridin-4-ones (Scheme 14).[29]

2.5.5. Reaction of Salicyl N-Tosylimines

The *aza*-Baylis−Hillman reaction of salicyl *N*-tosylimines with vinyl ketones produces generally a mixture of β-aminocarbonyl compounds and chromanes.[68] When DABCO was used as a catalyst, the reaction mostly gave chromanes in toluene, whereas switching to THF provided the *aza*-Baylis−Hillman adducts as the major products (Table 12). Electron-releasing groups on the salicyl moiety promote the formation of the *aza*-Baylis−Hillman adducts, whereas electron-withdrawing groups facilitate the formation of chromanes.

Scheme 17

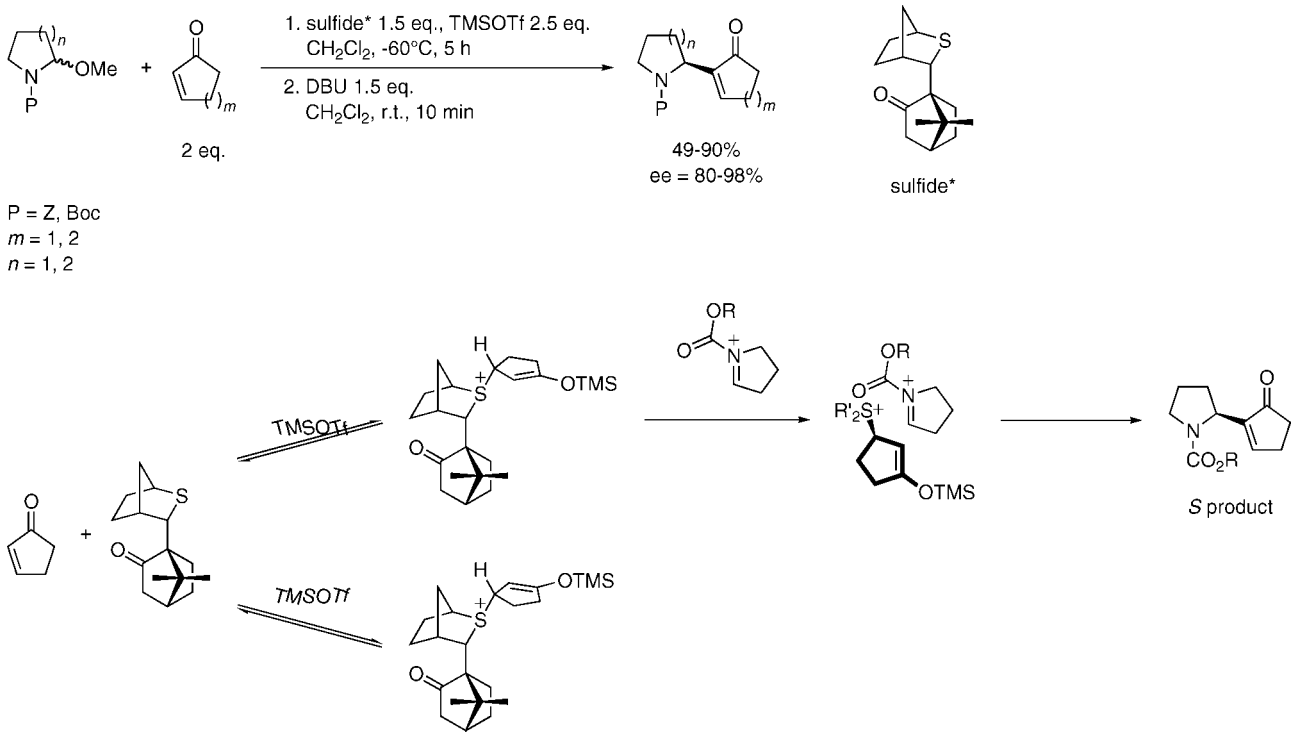
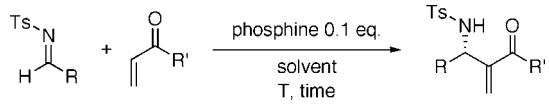


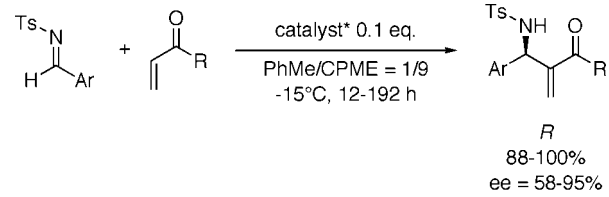
Table 17. Enantioselective *aza*-Morita−Baylis−Hillman Reaction



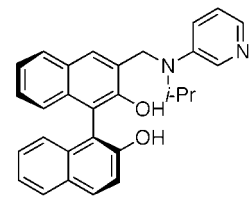
R′	phosphine	solvent	*T* (°C)	time (h)	yield (%)	ee (%)
Me	**LB 4**	THF	15	24−48	53−88	70−78
Me	**LB 5**	THF	−20	12−48	69−91	71−95
Me	**LB 6**	THF	−20	24−48	70−97	90−96
Me	**LB 7**[a]	THF	0	10−164	71−100	87−96
Me	**LB 8**	CH_2Cl_2	0	7−48	80−99	61−95
Et	**LB 8**	CH_2Cl_2	0	60	80−95	51−74
Me	**LB 8**	DCE	r.t.	12−60	75−99	46−93
Me	**LB 9**[b]	CH_2Cl_2	r.t.	5−80	61−98	67−97
Me	**LB 10**	CH_2Cl_2	0	24−48	72−98	68−87
Me	**LB 11**	CH_2Cl_2	r.t.	24−48	60−98	64−84
Me	**LB 12**	CH_2Cl_2	r.t.	24−48	64−98	35−91
Et	**LB 12**	CH_2Cl_2	r.t.	48	69−80	80−85
Me	**LB 13**	THF	−20	12−48	80−99	89−97
Et	**LB 13**	THF	−20	84−96	73−99	94−97
H	**LB 13**	THF	−20	12	83−90	89−94

[a] 1 mol % of phosphine was used. [b] Benzoic acid (0.05 equiv) was used as an additive.

Scheme 18



Ar = Ph, *p*-Tolyl, 4-Et-C_6H_4-, *p*-Anisyl, 4-F-C_6H_4-, 2-Cl-C_6H_4-, 3-Cl-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 3-O_2N-C_6H_4-, 4-O_2N-C_6H_4-, α-Np, β-Np, 2-Furyl
R = Me, Et, Ph, H



3. Stereoselective Synthesis

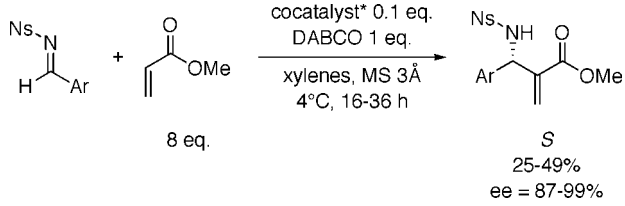
3.1. Use of Chiral Aldehydes

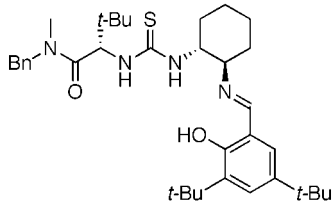
The first asymmetric synthesis of α-methylene-β-aminocarbonyl compounds was carried out by Kündig and co-workers.[69,70] It utilized chiral planar complexes of sulfonylimines derived from *ortho*-substituted benzaldehydes. These chiral aldehydes were first transformed into tosylimines and then reacted with a Michael acceptor in the presence of DABCO, to give α-methylene-β-amino esters or nitriles in good yields with good enantiomeric excesses (Scheme 15). The complexation with $Cr(CO)_3$ allows the discrimination of the two faces of the imine and increases its electrophilic character, which reduces considerably the reaction time. At the end of the reaction, a simple oxidation of the complex removes the $Cr(CO)_3$ group to liberate the α-methylene-β-amino ester or nitrile. The main disadvantage of this method is that it is limited to imines derived from *ortho*-substituted aldehydes.

3.2. Use of Chiral Bases

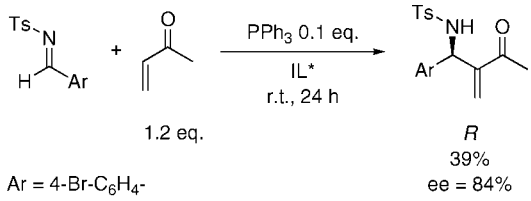
Since 2002, Shi and co-workers have started a systematic study of the asymmetric *aza*-Baylis−Hillman reaction[71,72] catalyzed by β-isocupreidine (β-ICD),[73,74] a chiral base

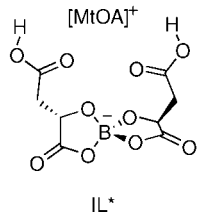
Scheme 19



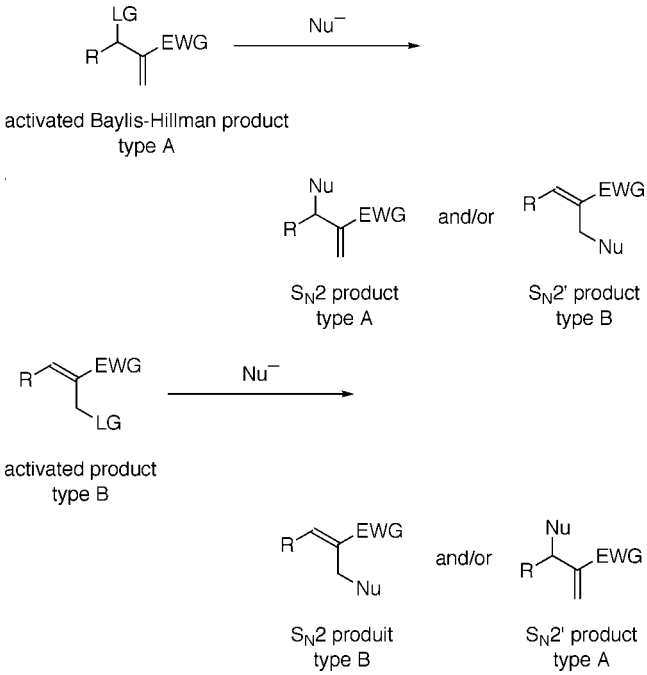


Scheme 20





Scheme 21



derived from quinidine (Figure 2). During this study, the reaction of aromatic tosylimines with simple Michael acceptors like methyl vinyl ketone, ethyl vinyl ketone, acrolein, methyl acrylate, acrylonitrile, or more hindered ones like phenyl acrylate and α-naphtyl acrylate was studied (Table 13). The enantioselectivities observed vary from medium to good. It should be noted that α,β-unsaturated ketones give compounds having a reverse absolute configuration compared to those obtained with other Michael acceptors studied therein.

The same catalyst was also used by the group of Adolfsson in the "one-pot" *aza*-Baylis−Hillman reaction with their own conditions.[75] In order to solubilize this base, isopropanol was replaced by THF. Reaction times were longer, but yields remained good and the reaction was still chemoselective (eq 12). On the other hand, enantiomeric excesses were not as good as those obtained by Shi and co-workers.

Scheme 22

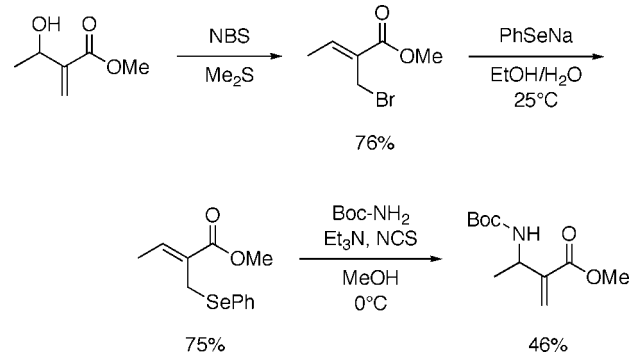
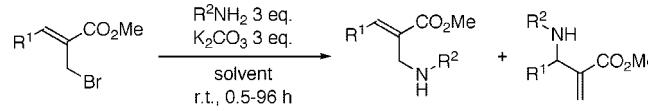
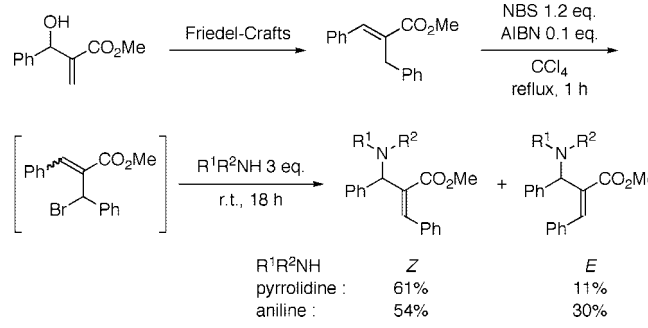


Table 18. Synthesis of β-Amino Esters by Nucleophilic Substitution

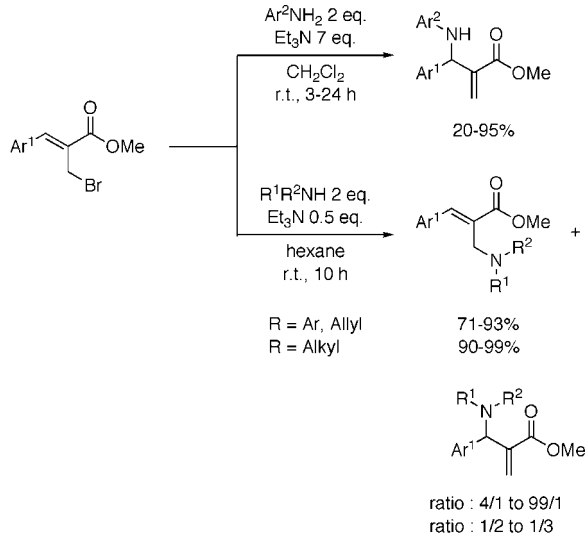


			yield (%)	
R^1	R^2	solvent	S_N2 product	S_N2' product
Ar	Ar	CH_3CN	59−76	0
		petroleum ether	47−64	13−21
Ar	Alk	CH_3CN	30−69	0−48
		petroleum ether	0	37−73
Alk	Alk	CH_3CN	42−89	0−31
		petroleum ether	0−60	10−72

Scheme 23

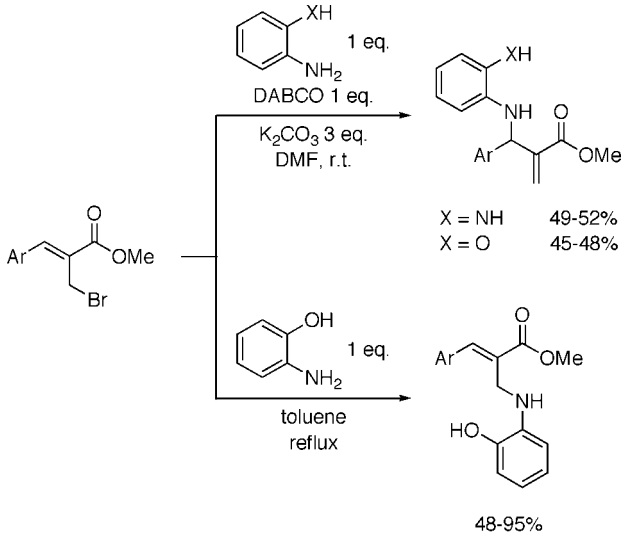


Scheme 24



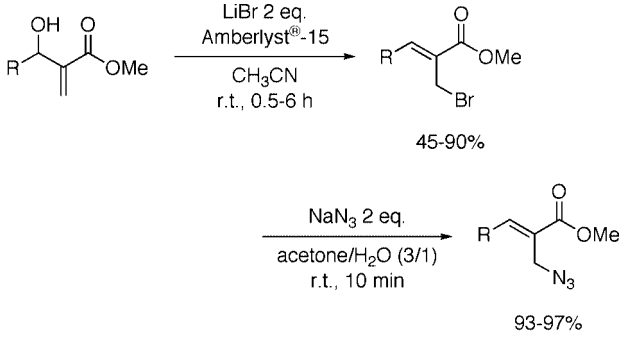
Ar^1 = Ph, *p*-Anisyl, 3-Br-C_6H_4-, α-Np, 2-Furyl, 2-Thienyl
Ar^2 = Ph, *p*-Anisyl, 2,4-Me_2-C_6H_3-
R^1R^2NH = $PhNH_2$, *p*-Anisidine, Allylamine, *n*-$BuNH_2$, Et_2NH, Morpholine

Scheme 25



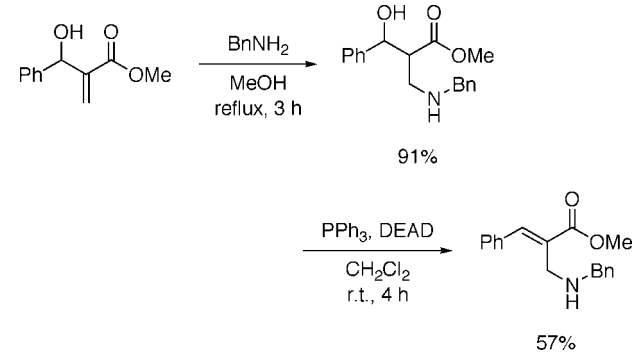
Ar = Ph, *p*-Tolyl, 2-Cl-C_6H_4-, 2-O_2N-C_6H_4-

Scheme 26

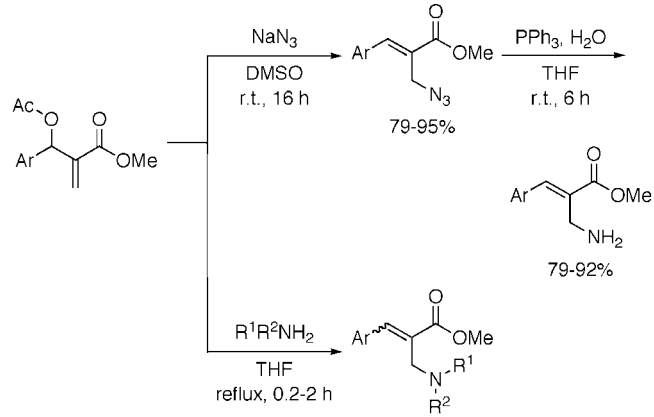


R = Ph, 3,4-(OCH_2O)-C_6H_3-, 2-Cl-C_6H_4-, β-Np, Cinnamyl, Me, *n*-Pr, *s*-Bu

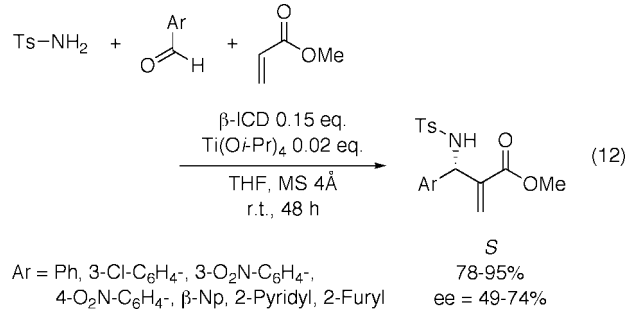
Scheme 27



Scheme 28



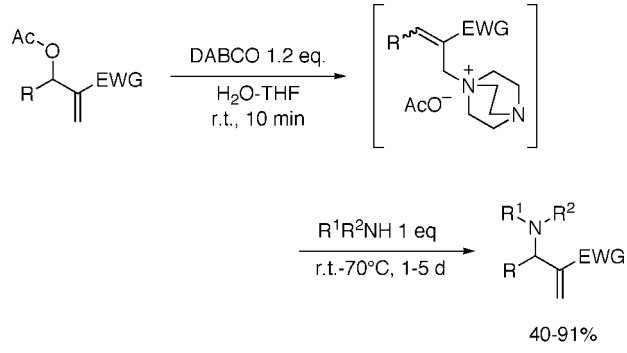
Ar = Ph, *o*-Anisyl, 2-Furyl, 2-Thienyl
R^1R^2NH = *i*-$PrNH_2$, $BnNH_2$, Me_2NH, $PhNH_2$



Ar = Ph, 3-Cl-C_6H_4-, 3-O_2N-C_6H_4-, 4-O_2N-C_6H_4-, β-Np, 2-Pyridyl, 2-Furyl

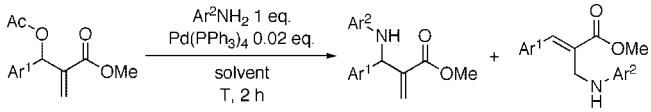
Hatakeyama and co-workers have extended their work concerning the Baylis−Hillman reaction of hexafluoroiso-

Scheme 29



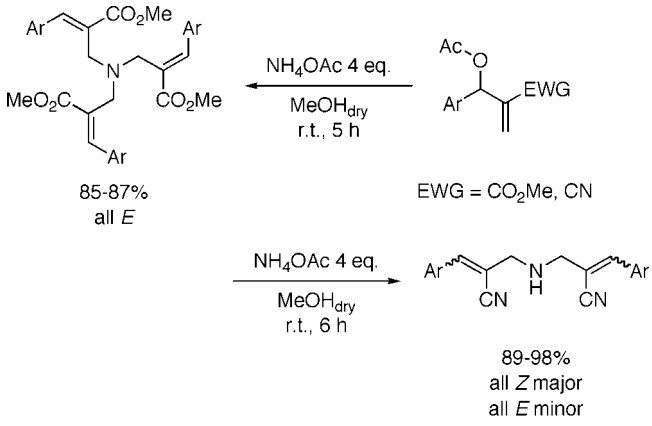
EWG = CO_2Et, CN
R = Ph, 2-F-C_6H_4-, 2-Cl-C_6H_4-, 2,4-Cl_2-C_6H_3-, 3-Pyridyl, *n*-Pentyl
R^1R^2NH = $TsNH_2$, $MsNH_2$, TsNHMe, PhthNH

Table 19. Allylic Amination by a Tsuji−Trost Reaction



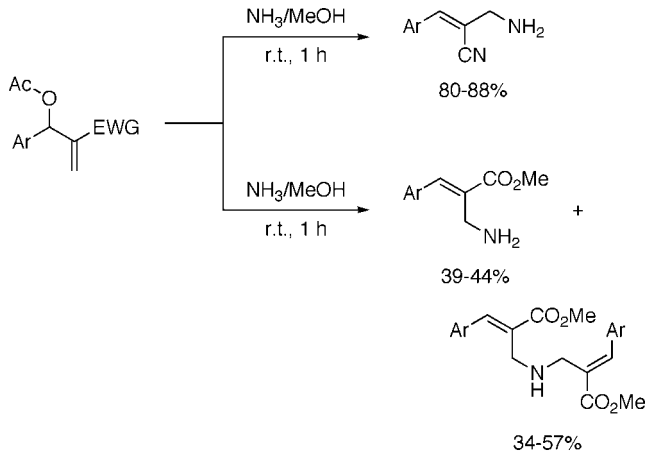
Ar^1	solvent	temperature	proportions A/B	yield (%)
Ph	CH_3CN	reflux	1:7 → 1:10	57−68
Ph	THF	r.t.	3:1 → 6:1	56−65
p-anisyl	THF	r.t.	90:10	66−76
4-Cl-C_6H_4−	THF	r.t.	15:85 → 2:98	68−78

Scheme 30



Ar = Ph, *p*-Tolyl, 2-F-C_6H_4-, 2-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2-Br-C_6H_4-

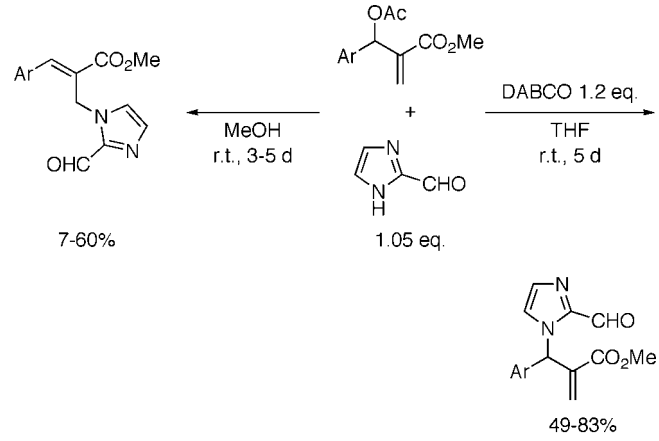
Scheme 31



Ar = Ph, *p*-Tolyl, 4-BnO-C_6H_4-, 2-F-C_6H_4-, 4-F-C_6H_4-, 2-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2-Br-C_6H_4-, α-Np, 2-Cl-C_6H_4-isoxazol-5-yl

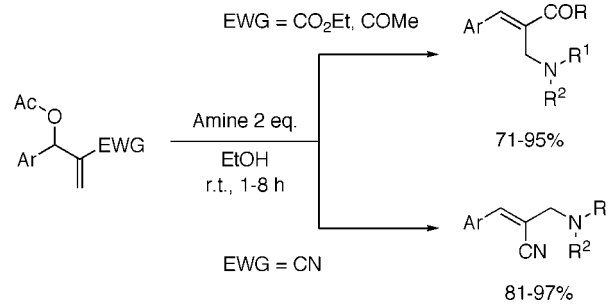
propyl acrylate catalyzed by β-isocupreidine[73] to the *aza*-version of this reaction.[76] Various imines were used, but as usual, the nitrogen atom must carry an electron-withdrawing group to activate the imine. Other bases like *O*-methyl-β-isocupredine and quinidine (Figure 2) were also tested, but poor results were obtained for both yield and selectivity. Among the imines tested, mesylimines and diphenylphosphinoylimines gave the best results. Because the diphenylphosphinoyl group was easily removable,[53] diphenylphosphinoylimines were used to complete the study (Table 14). Enantiomeric excesses obtained are modest, but they can be easily improved by a simple recrystallization.

Scheme 32



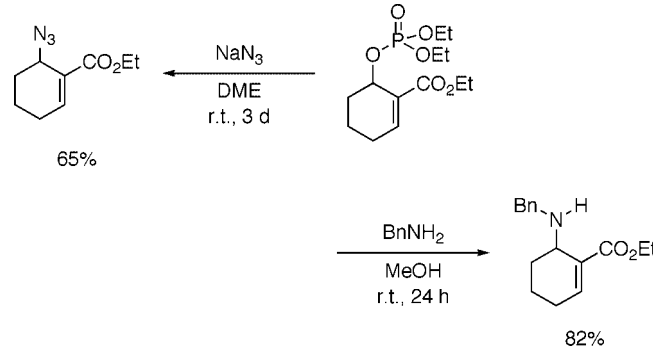
Ar = Ph, 4-F-C_6H_4-, 2-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2-Br-C_6H_4-

Scheme 33



Ar = Ph, 2-Br-C_6H_4-, 3-O_2N-C_6H_4-
Amine = *p*-Toluidine, *p*-Anisidine, $BnNH_2$, PhthNK, $TsNH_2$, Et_2NH, BnNHMe

Scheme 34



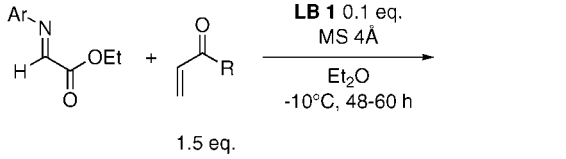
3.3. Use of Chiral Phosphines

Starting in 2002, Shi and co-workers explored the use of chiral phosphines to induce a selectivity in the *aza*-Morita−Baylis−Hillman reaction.[15,77] More recently, new chiral phosphines have been designed and synthesized to further improve the initial results.

A chiral phosphine derived from BINAP and bearing an hydroxyl group allowing the stabilization of the zwitterionic intermediates (Figure 3, Scheme 16) was tested successfully in the reaction of tosylimines with methyl vinyl ketone (Table 15).[15] Despite a long reaction time, yields were good and enantiomeric excesses were promising. On the other hand, the use of phenyl acrylate, which allowed certainly faster reaction, was relatively disappointing. This is general for acrylates since methyl acrylate and naphthyl acrylates did not give good results either. Acrolein reacted rather quickly

to provide the *aza*-Baylis−Hillman product in good yield and enantioselectivity.

This chiral phosphine **LB 1** gives also a very efficient reaction of ethyl (arylimino)acetates with methyl vinyl ketone and ethyl vinyl ketone.[78] In most cases, the *aza*-Baylis−Hillman adducts are produced in good yields and high enantiomeric excesses (eq 13).



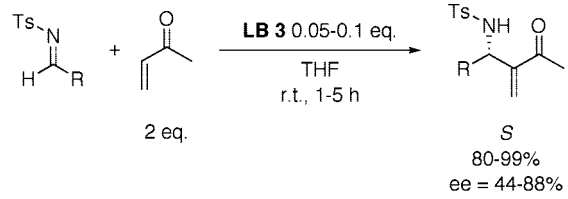
(13)

R = Me, Et
Ar = Ph, *m*-Tolyl, *p*-Tolyl, *p*-Anisyl, 4-F-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 3-F_3C-C_6H_4-, 4-Cl-2-MeO-C_6H_3-

53-99%
ee = 66-97%

Other phosphines of the same type were also tested but gave poor results. Thereafter, the same group tried enantioselective reactions with cyclopentenone and cyclohexenone as Michael acceptors.[79] In this case, a new phosphine, **LB 2**, more nucleophilic than the previous one, was employed. Yields were rather good, but enantiomeric excesses were poor, in particular with cyclohexenone (Figure 3, Table 16).

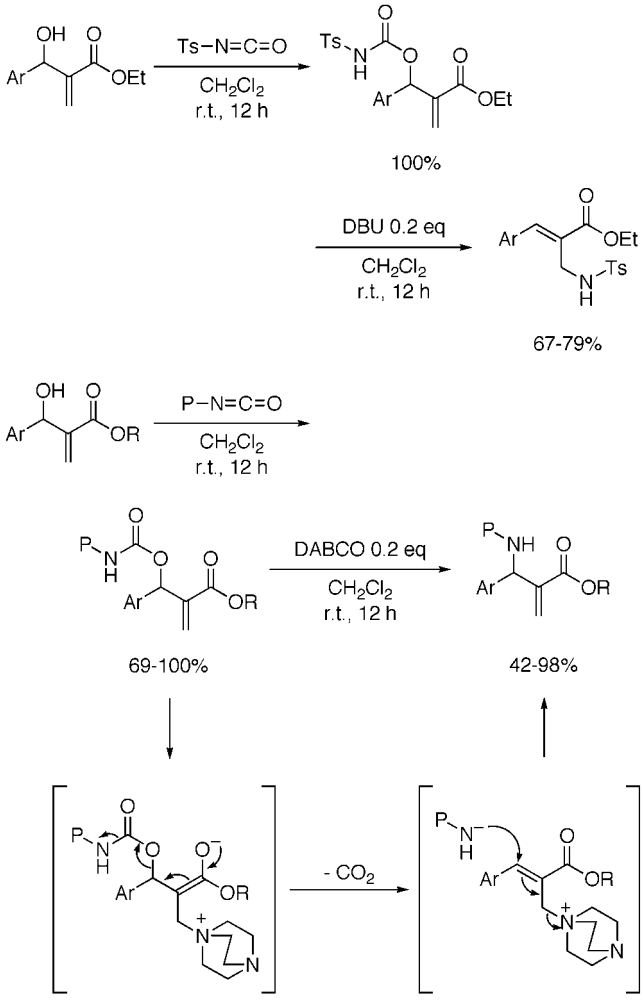
A slight modification of the phosphine **LB 1** by replacement of a phenyl group by an alkyl chain allows a drastic reduction of the reaction time. The best results were obtained with the phosphine **LB 3** bearing a butyl chain (Figure 3), but in most cases, lower enantioselectivities were observed (eq 14).[80]



(14)

R = Ph, *p*-Tolyl, *p*-Anisyl, 2-F-C_6H_4-, 2-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2-Br-C_6H_4-, 3-Br-C_6H_4-, 4-Br-C_6H_4-, 2,4-Cl_2-C_6H_3-, 2-O_2N-C_6H_4-, 3-O_2N-C_6H_4-, 4-O_2N-C_6H_4-, α-Np, 2-Furyl, Cinnamyl

Scheme 35



Ar = Ph, *p*-Anisyl, 4-Cl-C_6H_4-, 4-O_2N-C_6H_4-, β-Np
R = Me, Et, *t*-Bu
P = Ts, PhCO, Cl_3CCO, Boc, Z

In order to improve the results obtained previously, the same group undertook the modification of the chiral phosphine **LB 1**. Thus, two new phosphines **LB 4** and **LB 5** (Figure 3), bearing long polyfluoroalkyl chains, were prepared and tested in the *aza*-Morita−Baylis−Hillman reaction of methyl vinyl ketone with aromatic tosylimines (Table 17).[81] The phosphine **LB 5** gave comparable results to those obtained with phosphine **LB 1**.

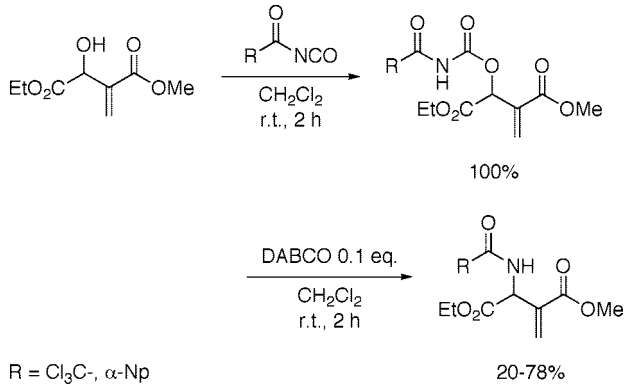
Recently, the group of Shi has developed a new chiral phosphine **LB 6** bearing several hydroxy groups, creating hydrogen bonds that allow the stabilization of the zwitterionic intermediate (Figure 3).[82] Yields were good and enantiomeric excesses in the reaction of methyl vinyl ketone with sulfonylimines were higher than those obtained with phosphine **LB 1** (Table 17). Further improvements in this family of catalysts have been made by Ito and co-workers.[83] The replacement of the binaphthol unit of **LB 6** by a phenol produces a new organocatalyst **LB 7** (Figure 3) with a higher catalytic activity and giving similar results in terms of yields and enantioselectivities to those obtain by Shi for **LB 6**.[82] These results were obtained with only 1 mol % of catalyst **LB 7** (Table 17).

Amide groups could also act as efficient hydrogen-bonding donors. Thus, the groups of Shi and Li used this feature to design a new class of chiral phosphine catalysts.[84] The replacement of the hydroxyl group in the phosphine **LB 1** by an amide function gave a new chiral phosphine **LB 8** (Figure 3) that resulted in good yields and moderate-to-good enantioselectivities in the reaction of vinyl ketones with tosylimines (Table 17).

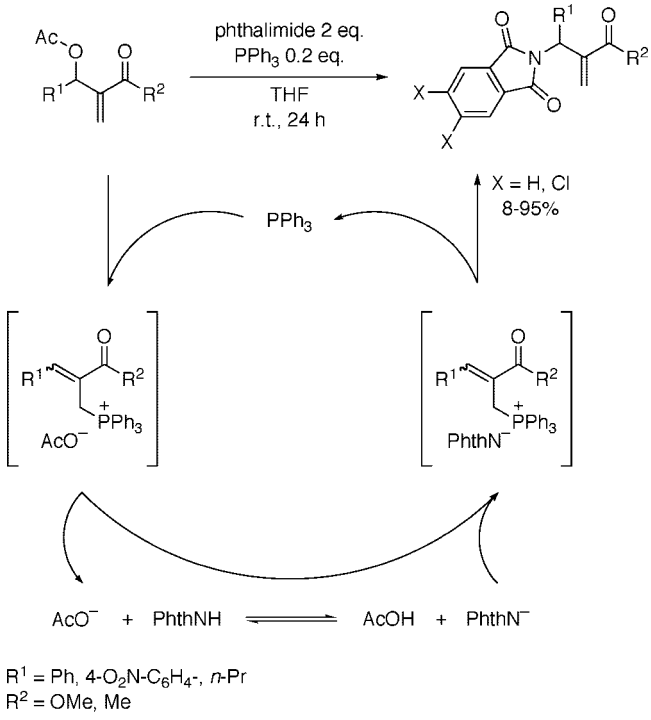
Zwitterionic intermediates stabilization can also take place with a thiourea unit. Thus, Shi and co-workers combined advantageously the BINAP unit and a thiourea moiety to produce a new phosphine/thiourea catalyst **LB 9** (Figure 3).[85] Good yields and moderate-to-good enantioselectivities were obtained in the *aza*-Baylis−Hillman reaction of methyl vinyl ketone with tosylimines catalyzed by this phosphine/thiourea in the presence of benzoic acid (Table 17).

Recently, polymeric phosphines were developed by Shi and co-workers and tested in the *aza*-Morita−Baylis−Hillman reaction of vinyl ketones and acrolein with tosylimines. A first series of sterically congested phosphine−amide bifunctional organocatalysts **LB 10**, **LB 11**, and **LB 12** based on phosphine **LB 8** gave similar results to those

Scheme 36



Scheme 37



obtained with other phosphines.[86] However, the best results were obtained with the phosphine **LB 13**, the best member of the second family, based on phosphine **LB 7** (Figure 3 and Table 17).[87]

3.4. Use of a Chiral Sulfide

Aggarwal and co-workers have employed a chiral sulfide in the *aza*-Baylis−Hillman reaction of in situ generated iminium ions with various α,β-unsaturated ketones (Scheme 17).[60] While cyclic enones provide the adduct with good yields and enantioselectivies, the use of acyclic enones like methyl vinyl ketones gave the adduct with poor ee. The authors have shown by low-temperature NMR studies that a dynamic equilibrium between the starting material and the two diastereomeric enol ethers exists at the reaction temperature. One of the diastereomers, for an unknown reason, reacts preferentially with the iminium ion (pathway shown in Scheme 17), the most favored approach providing essentially the *S* enantiomer of the product.

3.5. Use of an Organocatalyst Derived from BINOL

In order to improve the results obtained, the group of Sasai has developed a new catalyst derived from BINOL.[88,89] Like β-isocupreidine and the chiral phosphines, this base contains both a subunit possessing a Lewis base character and two hydroxyl groups displaying a Brønsted acid character, to ensure the stabilization of the zwitterionic intermediates. Although the reaction times are rather long, yields and enantioselectivities are good (Scheme 18).

3.6. Use of a Chiral Ligand Derived from Thiourea

Recently, Jacobsen showed that the use of a chiral cocatalyst derived from thiourea, in addition to DABCO, allows the synthesis of α-methylene-β-amino esters in modest yields but with good enantiomeric excesses (Scheme 19).[14] It was also shown that a longer reaction time improved the yield but decreased considerably the enantiomeric excess.

3.7. Use of Chiral Ionic Liquids

Leitner and co-workers showed very recently that chiral ionic liquids prepared from L-(−)-malic acid allowed a very good enantioselectivity in the *aza*-Morita−Baylis−Hillman reaction of methyl vinyl ketone with tosylimines (Scheme 20).[90] This ionic liquid possess two acidic sites, allowing interactions with the enolate intermediate, which is responsible for the enantioselectivity.

4. Alternative Access Pathways to β-Aminocarbonyl Compounds

The *aza*-Baylis−Hillman reaction has some limits related to the nature of the imine. If aromatic imines are generally good coupling partners in this type of reaction, it is not the case of aliphatic ones, for which rare examples have been reported. Moreover, no group except Adolfsson and coworkers specifies the quantity of hydroxylated products formed. The reaction is rarely complete, and a purification step is required.

Other groups found it easier to use the Baylis−Hillman products as precursors of the β-aminocarbonyl derivatives. This presents the advantage of extending the reaction to aliphatic aldehydes, and even if the reaction is not total, the purification is generally easier. Some miscellaneous access routes to β-aminocarbonyl derivatives will be also described.

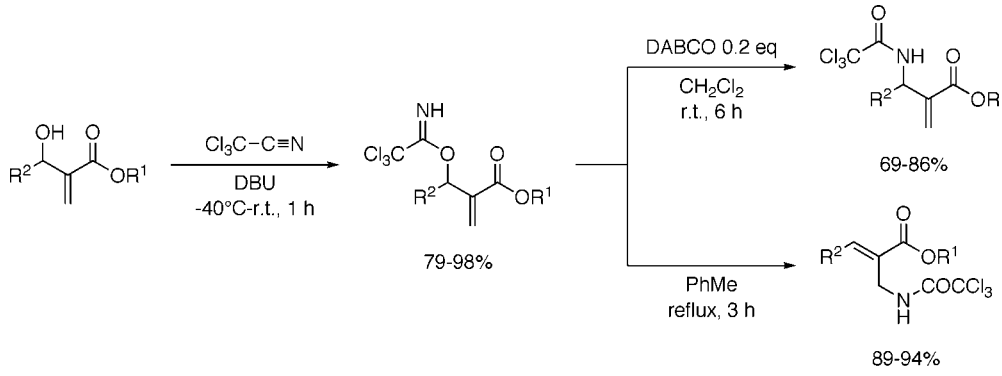
4.1. Starting from Baylis−Hillman Products

The use of Baylis−Hillman products to carry out the synthesis of β-aminocarbonyl derivatives requires first of all the activation of the alcohol function as a bromide, an acetate, or another leaving group. It can also be activated under acid catalysis. The reaction can occur on the traditional Baylis−Hillman adducts of type A (1,1-disubstituted olefins) or on the type B derivatives (1,1,2-trisubstituted olefins). Depending on the reaction conditions, it is possible to obtain either the nucleophilic substitution product or the allylic substitution product (Scheme 21).

4.1.1. Via the Formation of an Allylic Bromide

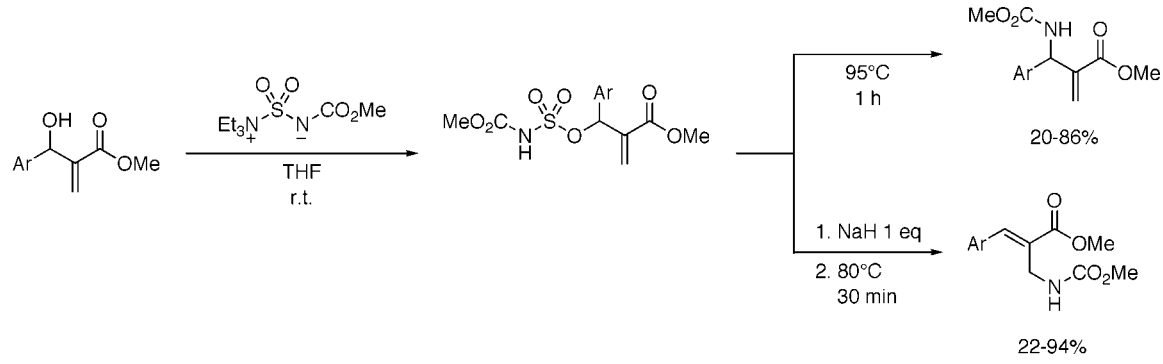
The first alternative access pathway was proposed by the group of Brown.[91] The allylic alcohol was first transformed

Scheme 38



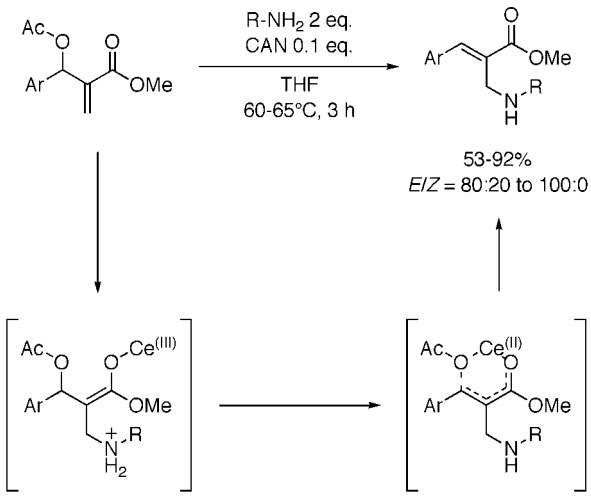
R^1 = Me, Et, *t*-Bu
R^2 = Ph, 4-Cl-C_6H_4-, 4-O_2N-C_6H_4-, β-Np, *i*-Bu, *i*-Pr, Me, H

Scheme 39



Ar = Ph, *p*-Tolyl, *p*-Anisyl, 2-Cl-C_6H_4-, 4-Cl-C_6H_4-, 3-O_2N-C_6H_4-, 4-O_2N-C_6H_4-

Scheme 40

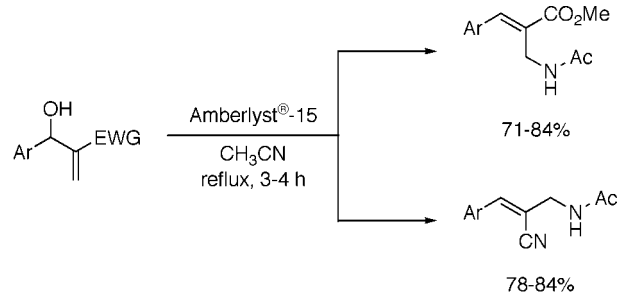


Ar = Ph, *p*-Tolyl, 4-Cl-C_6H_4-
R = Ph, *p*-Tolyl, *p*-Anisyl, 4-O_2N-C_6H_4-, 3-Cl-4-Me-C_6H_3-, Bn, α-Np, Me, *n*-C_8H_{17}-, *n*-$C_{16}H_{33}$-, CyHx,

by the action of NBS into a type B bromide, which was then transformed into the corresponding selenide. A [2,3]-sigmatropic rearrangement in the presence of Boc-NH_2 and NCS provided the β-amino ester in a modest yield (Scheme 22).

Hoffmann has submitted these type B bromides to the action of various amines in the presence of K_2CO_3 (Table 18).[92] The results obtained are strongly dependent on the nature of the bromide and the solvent used. In most of the cases, when the reaction was carried out in acetonitrile, only the

Scheme 41



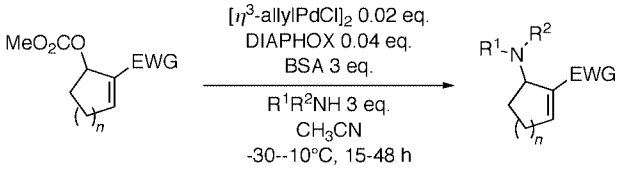
EWG = CO_2Me, CN
Ar = Ph, *p*-Tolyl, *p*-Anisyl, 3,4-$(MeO)_2$-C_6H_3-, 2-Cl-C_6H_4-, 4-Cl-C_6H_4-, 2,4-Cl_2-C_6H_3-, 3-O_2N-C_6H_4-

S_N2 products were obtained. In contrast, the S_N2' product was favored in petroleum ether but the S_N2' selectivity was lost for aromatic amines.

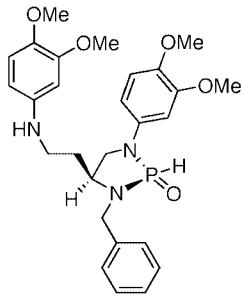
The group of Kim has described the synthesis of β-substituted β-amino esters by displacement of bromides with pyrrolidine and aniline.[93] Bromination of methyl 2-benzylcinnamate, obtained by a Friedel−Crafts reaction on a Baylis−Hillman alcohol, gave a mixture of *E* and *Z* allylic bromides. Nucleophilic displacement of the bromide occurs either in a S_N2 or S_N2' fashion, but the use of a "symmetric" substrate simplified the outcome of the reaction, and only mixtures of *Z* and *E* type A β-amino esters were obtained (Scheme 23).

Recently, Lee and co-workers carried out the synthesis of β-amino esters by nucleophilic substitution on type B allylic bromide.[94] Carried out in dichloromethane in the presence

Scheme 42

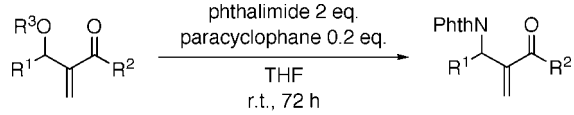


EWG = CO_2Me, CONHBn, CON(OMe)Me, CN
n = 1-3
R^1R^2NH = $BnNH_2$, 4-Methoxybenzylamine, 2-Furfurylamine, Allylamine, *i*-$PrNH_2$, N^{in}-Boc-Tryptamine, Morpholine, *p*-Anisidine

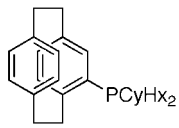


DIAPHOX

Scheme 43

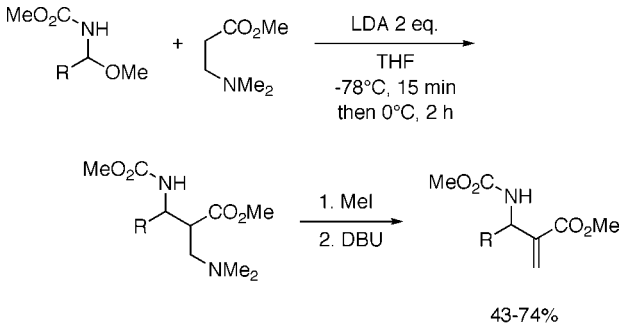


R^1 = Ph, *p*-Anisyl, 4-Cl-C_6H_4-, 4-O_2N-C_6H_4-, Et, *i*-Pr
R^2 = OMe, OEt, O*t*-Bu, Me
R^3 = Ac, Boc



(*R*)-paracyclophane

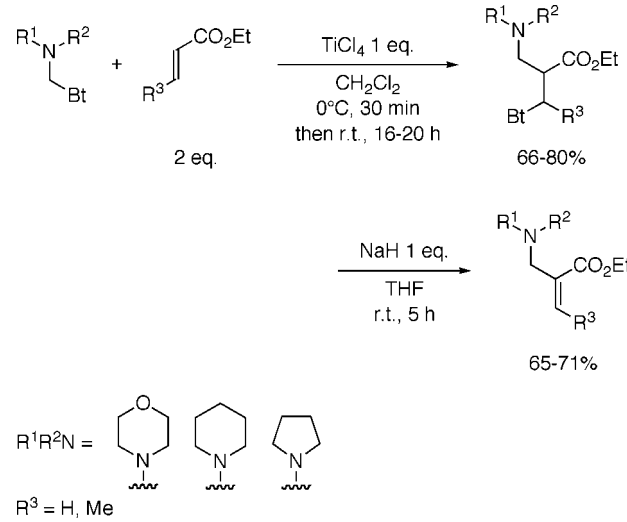
Scheme 44



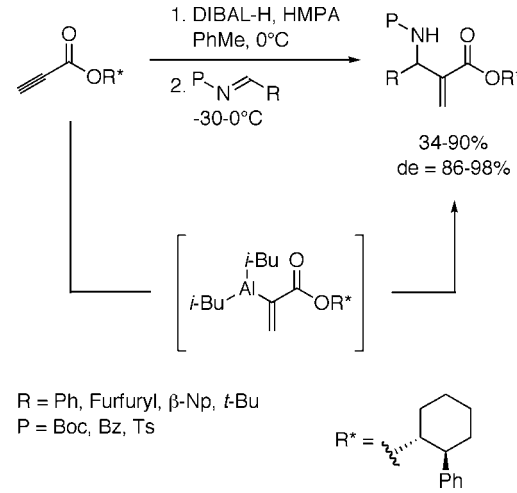
R = Me, *i*-Pr, *i*-Bu, *t*-Bu

of triethylamine, the substitution occurred only at the allylic position. On the other hand, in hexane, the reaction gave a mixture of type A and B β-amino esters, with type B β-amino ester being the major compound when anilines or allylamine

Scheme 45

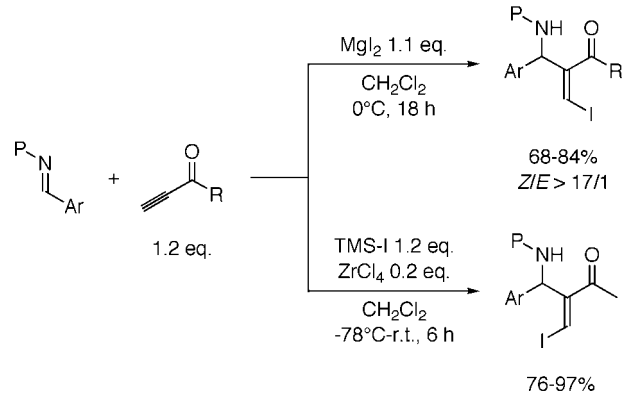


Scheme 46



Scheme 47

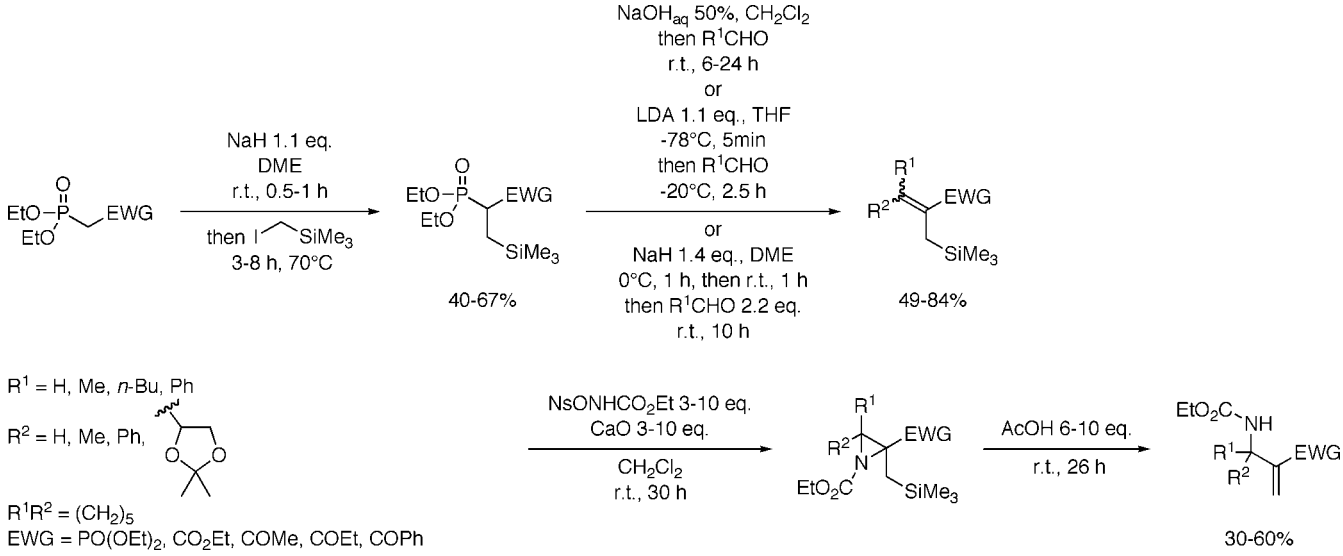
Ar = Ph, *p*-Tolyl, *p*-Anisyl, 3-BnO-C_6H_4-, 4-F-C_6H_4-, 4-Cl-C_6H_4-, 2-Furyl, 2-Thienyl
P = Ts, Ms, Bs
R = Me, OMe, OEt



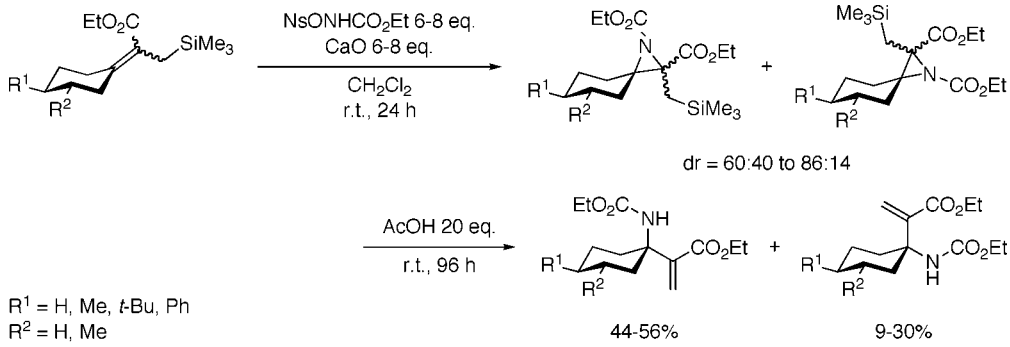
Ar = Ph, 4-Cl-C_6H_4-, 2,4-Cl_2-C_6H_3-, 4-O_2N-C_6H_4-
P = Ph, 4-Br-C_6H_4-, 3-F_3C-C_6H_4-
R = Me

are used (Scheme 24). It should be noted that the use of aliphatic amines reverses the regioselectivity, but with poor results.

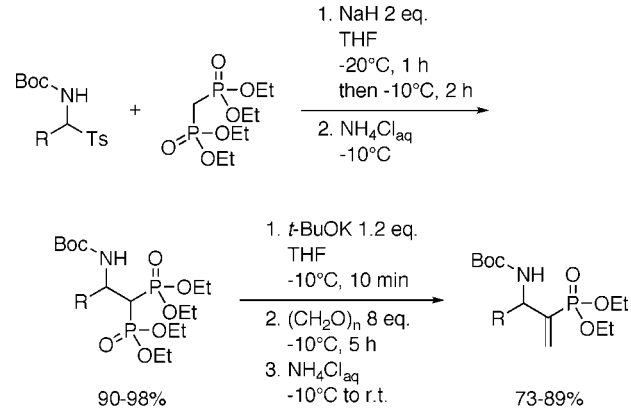
Scheme 48



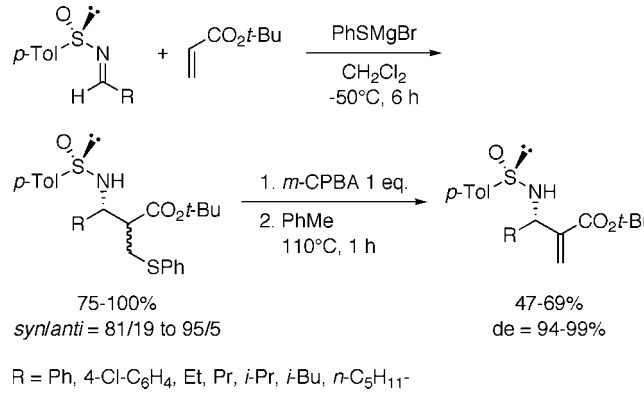
Scheme 49



Scheme 50



Scheme 51



Similar transformations have been described by Perumal and co-workers using various symmetric and nonsymmetric anilines (Scheme 25).[95]

Type B bromides have also been used as precursors of type B β-azido esters by the group of Sá.[96] Various bromides were efficiently prepared from type A β-hydroxy esters under heterogeneous catalysis conditions using LiBr as the bromide source in the presence of Amberlyst-15. The S_N2 substitution of the bromide using sodium azide in a mixture of acetone and water afforded the corresponding azido derivatives in excellent yields (Scheme 26). The type B bromides have proven to be very reactive in this transformation compared to type A and B acetates under any given conditions.

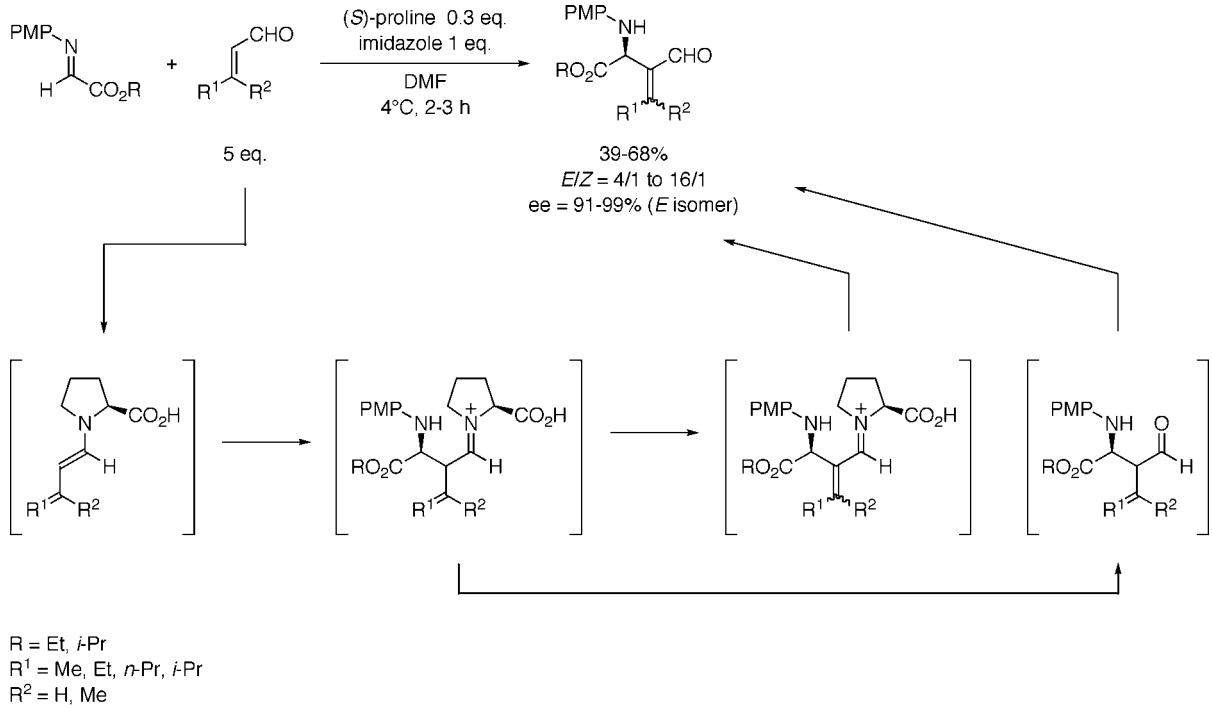
4.1.2. Via a Conjugate Addition

A type B β-amino ester has also been obtained by the group of Ganesan under Mitsunobu reaction conditions.[97] In this case, an elimination occurred instead of the expected intramolecular Mitsunobu reaction originally designed to lead to the formation of an azetidine (Scheme 27).

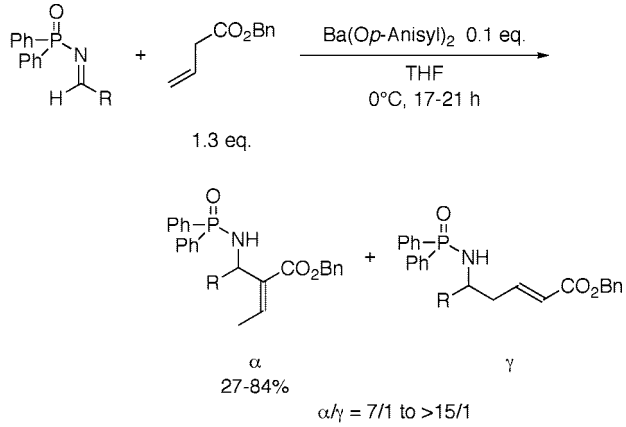
4.1.3. Allylic Amination of Baylis−Hillman Products

A more effective procedure was developed by the group of Foucaud.[98] First, the allylic alcohol was activated as an acetate, which was then subjected to nucleophilic attack by

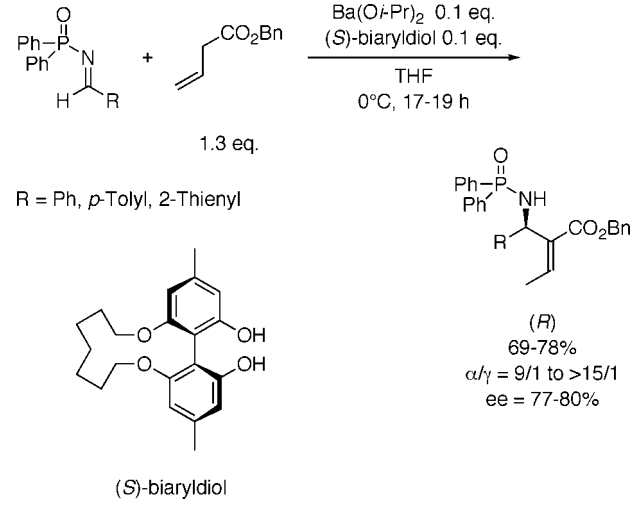
Scheme 52



Scheme 53



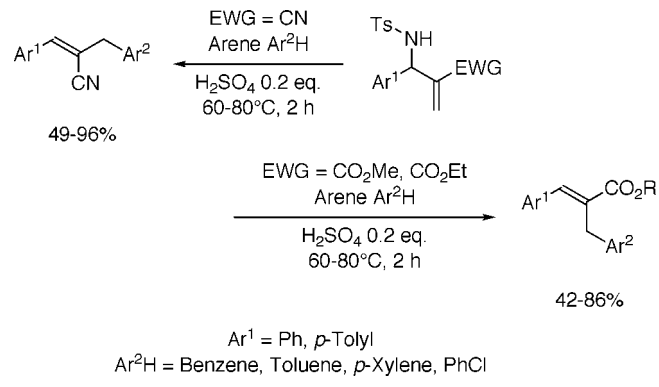
Scheme 54



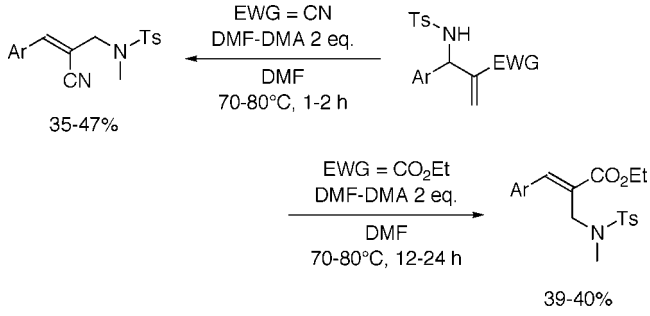
sodium azide or benzylamine. The attack occurred preferentially according to a S_N2' reaction rather than a S_N2 reaction, with the type B product thus obtained being mainly in *E* configuration (Scheme 28).

A similar transformation has also been described by the group of Batra via the formation of a DABCO salt intermediate.[99] These new conditions allowed the formation of the type B azides in a very efficient manner and in short reaction times (eq 15). Addition of sodium azide in water on Baylis−Hillman acetates afforded the same type B β-azidocarbonyl compounds in good yields (eq 16).[100] Acetates derived from β-hydroxy esters gave exclusively *E* compounds, whereas acetates derived from β-hydroxy nitriles gave exclusively *Z* compounds.

Scheme 55



Scheme 56



Scheme 57

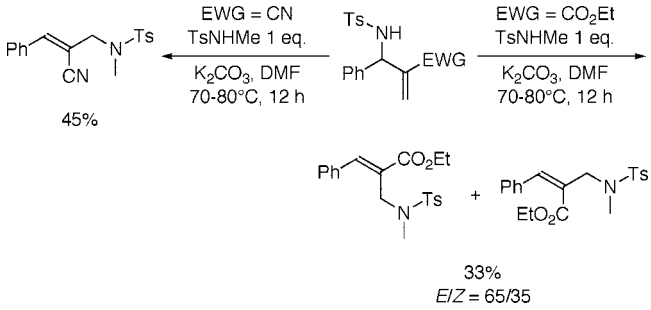
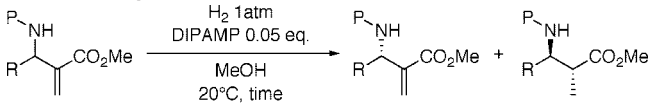


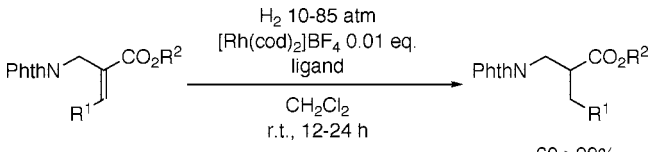
Table 20. Kinetic Resolution by Directed Hydrogenation of α-Methylene-*β*-Amino Esters



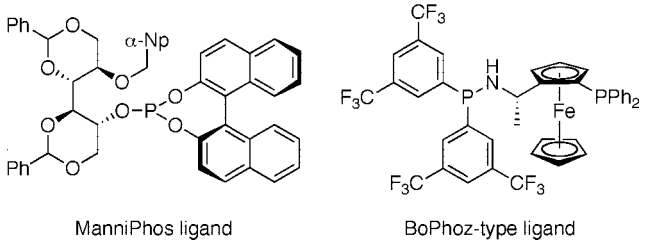
P	R	τ (%)	time (min)	ee (%)
			S	*RR*
Boc	Me	56	60	87[a]
Ac	Me	58	50	96[b]
Boc	Et	60	90	98[a]

[a] ee of the product. [b] ee of the recovered starting material.

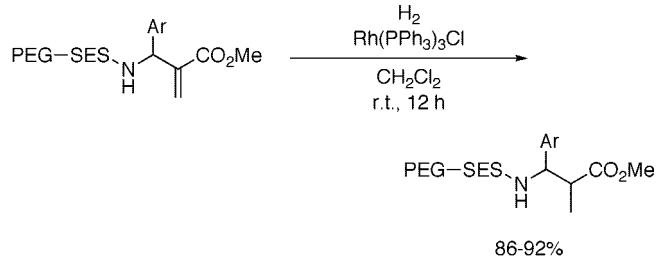
Scheme 58



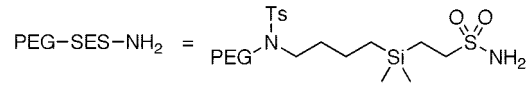
R^1 = H, Ph, *p*-Tolyl, *o*-Anisyl, *p*-Anisyl, 4-F-C_6H_4-, 4-Cl-C_6H_4-, 4-F_3C-C_6H_4-, 2-Thienyl, *i*-Pr
R^2 = Me, Et



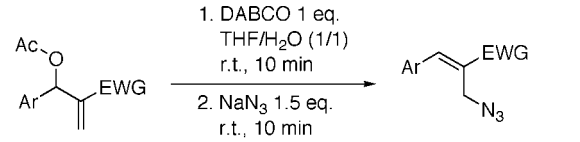
Scheme 59



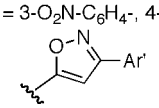
PEG−OH = $H(OCH_2CH_2)_nOH$ with an average MW = 3400



Ar = Ph, 3,5-$(MeO)_2$-C_6H_3-, 4-MeO_2C-C_6H_4-, 2-Furyl-

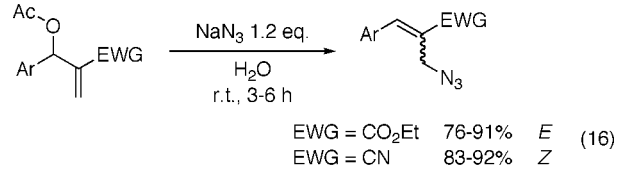


EWG = CO_2Me, CO_2Et, CO_2n-Bu, CO_2t-Bu, CN, COMe
Ar = 3-O_2N-C_6H_4-, 4-O_2N-C_6H_4-, 4-F_3C-C_6H_4-,



Ar' = Ph, *p*-Tolyl, 2-BnO-C_6H_4-, 2-Cl-C_6H_4-, 3-O_2N-C_6H_4-

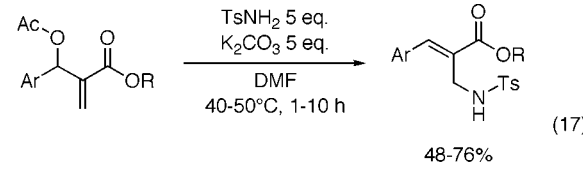
The group of Kim has brought an important contribution



EWG = CO_2Et, CN
Ar = Ph, *p*-Anisyl, 4-F-C_6H_4-, 3-O_2N-C_6H_4-, α-Np, 2-Furyl, 2-Thienyl, Et, *n*-C_9H_{19}-

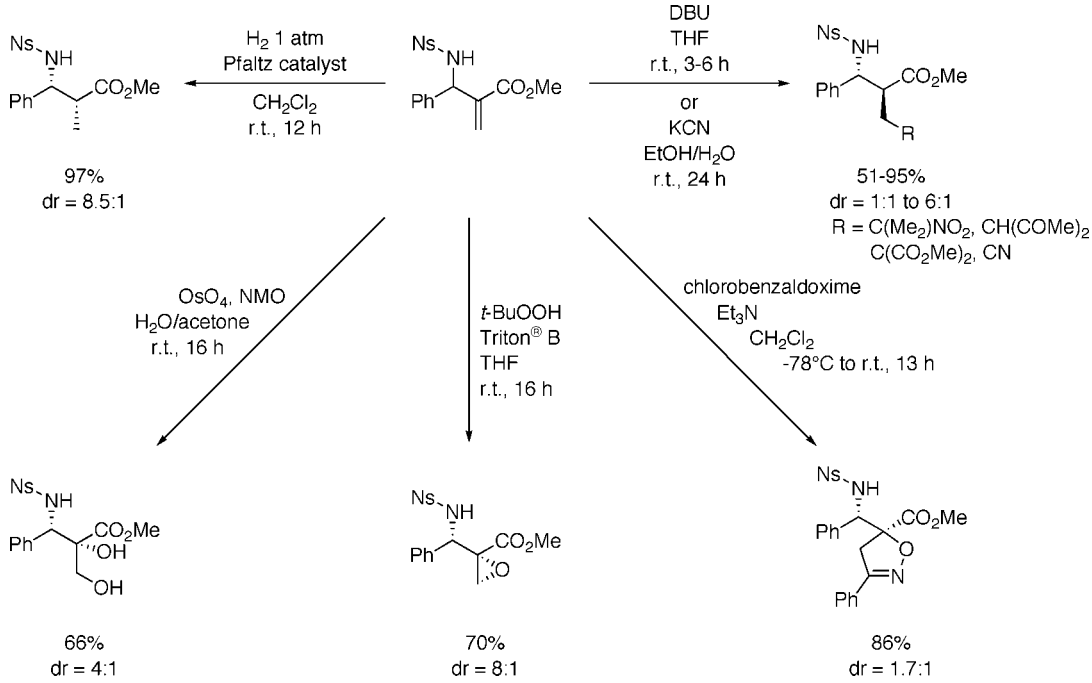
in the study of the reactivity of Baylis−Hillman acetates.[101,102] Reaction of Baylis−Hillman acetates with DABCO and then with a nitrogen nucleophile gives the type A *aza*-Baylis−Hillman product by a double nucleophilic allylic substitution (Scheme 29). The reaction can be carried out with various amine precursors like tosylamine, mesylamine, tosylmethylamine, or phthalimide.

This group has also shown that, in the absence of DABCO, treatment of Baylis−Hillman acetates by tosylamine in the presence of K_2CO_3 provides only type B *β*-amino esters (eq 17).[103,104]

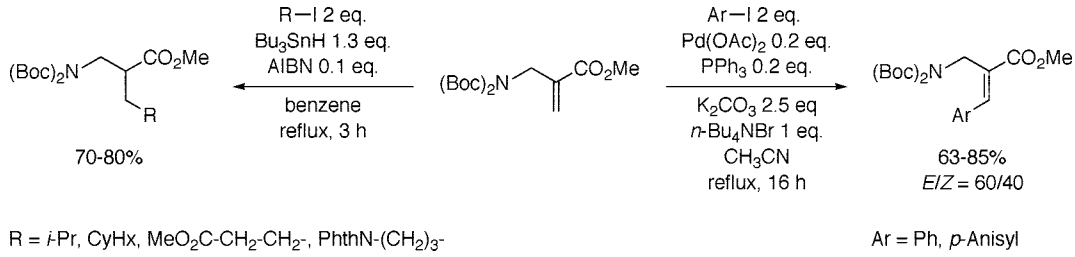


Ar = Ph, *p*-Tolyl, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 2,4-Cl_2-C_6H_3-
R = Me, Et

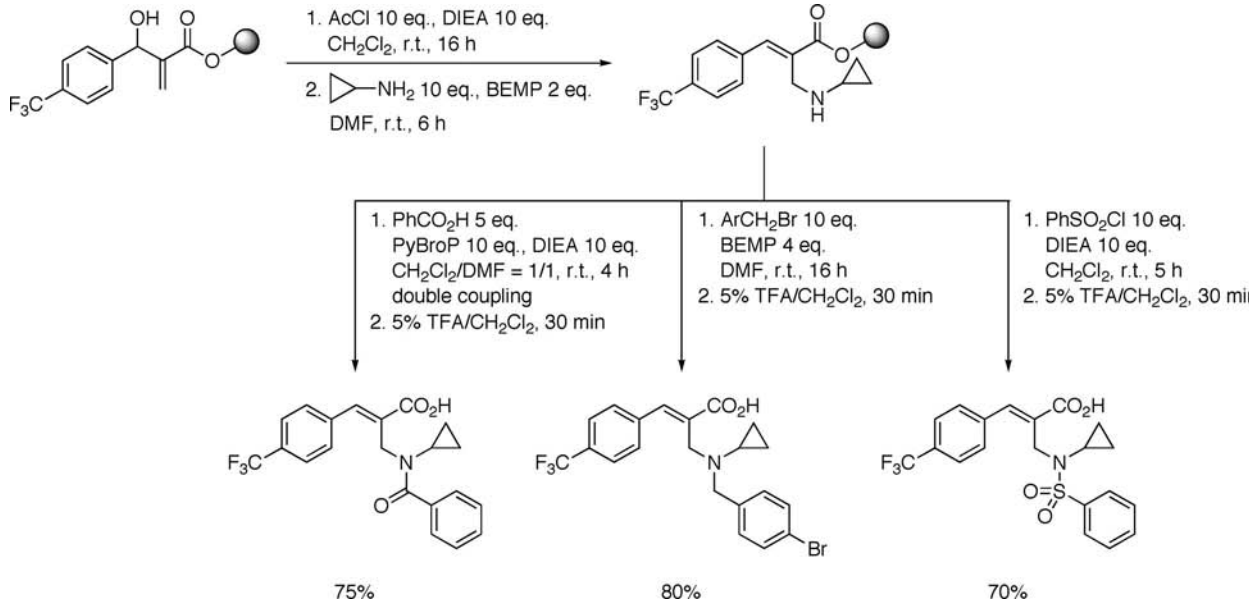
Scheme 60



Scheme 61



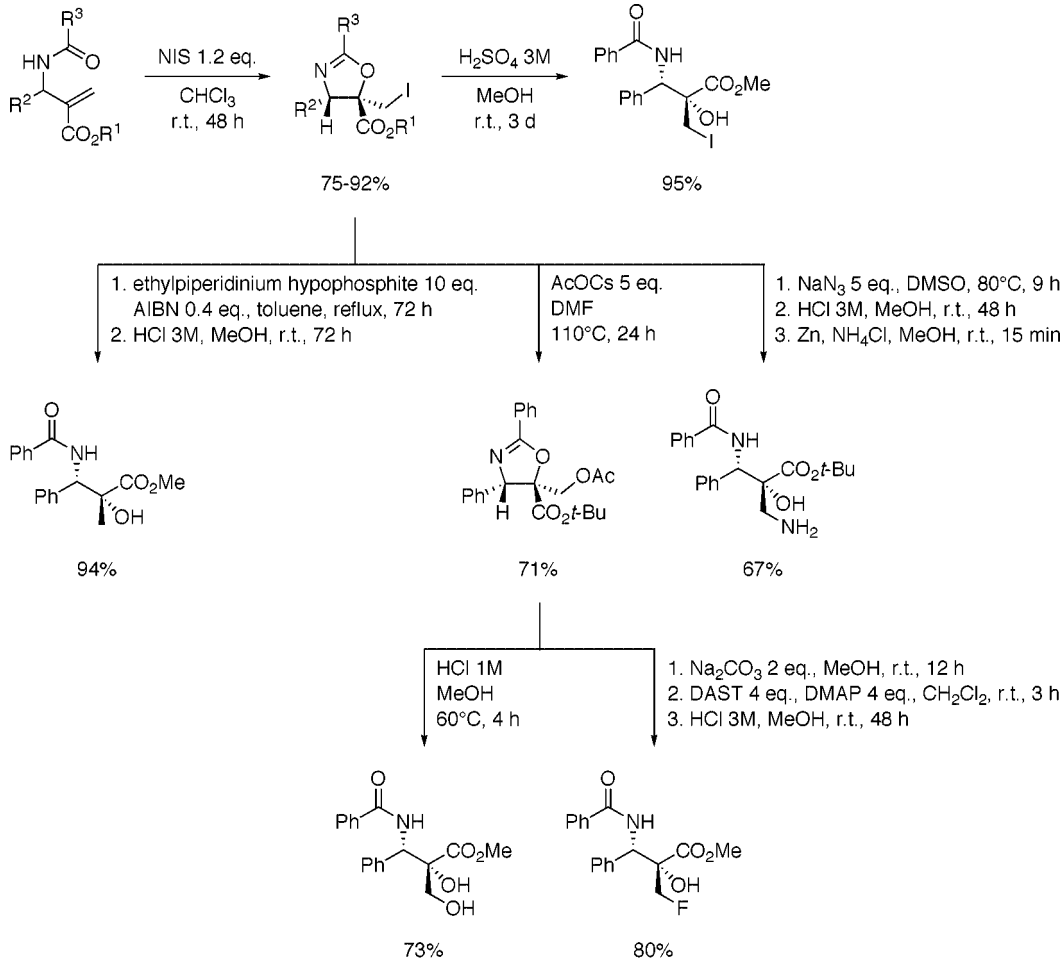
Scheme 62



Iqbal and co-workers carried out the synthesis of β-amino esters by a Tsuji−Trost reaction.[105] The reaction provides mixtures of type A and B products, in proportions that vary according to the reaction conditions, to the nature of the Baylis−Hillman product, and, to a lesser extent, to the aniline used (Table 19).

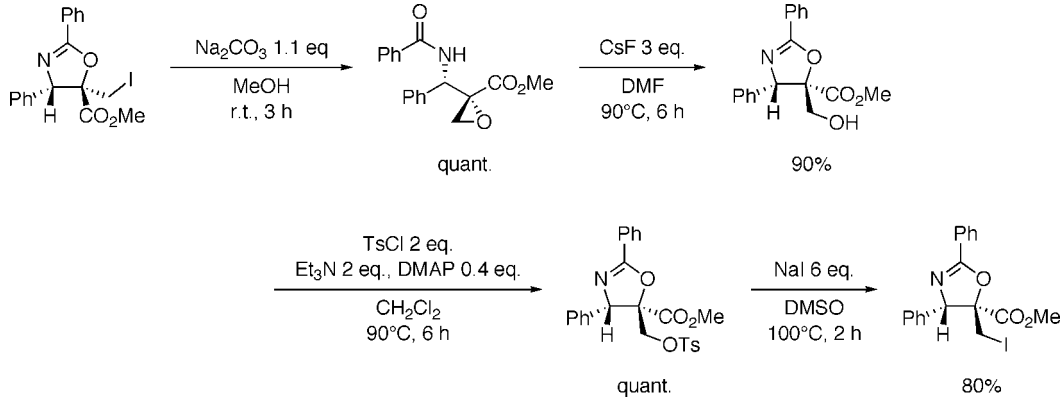
Although Das and co-workers claimed that action of ammonium acetate on the Baylis−Hillman acetates gave primary type B β-aminocarbonyl compounds,[106] the group of Batra demonstrated that, under these conditions, the reactions gave tertiary type B β-amino esters or secondary type B β-amino nitriles (Scheme 30).[107] In both cases, the

Scheme 63



R^1 = Me, Et, *t*-Bu
R^2 = Ph, *p*-Anisyl, 4-Cl-C_6H_4-, 4-O_2N-C_6H_4-
R^3 = Ph, *t*-Bu, Bn, $ClCH_2$, Cl_3C

Scheme 64

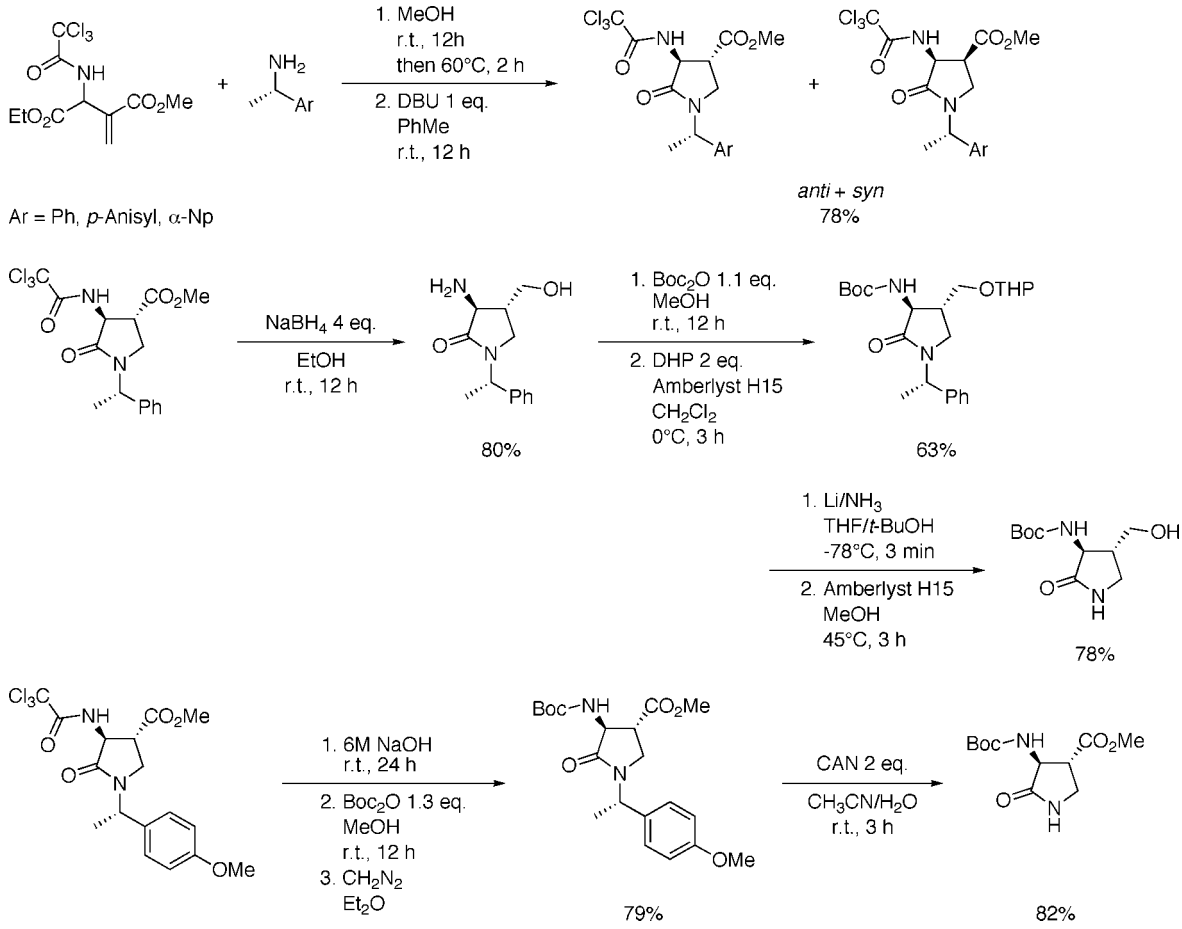


reaction provided the nucleophilic allylic substitution products in good yields. When the reaction was carried out on esters, the reaction gave exclusively all *E* compounds. On the other hand, when the reaction was carried out on nitriles, all *Z* compounds were largely favored.

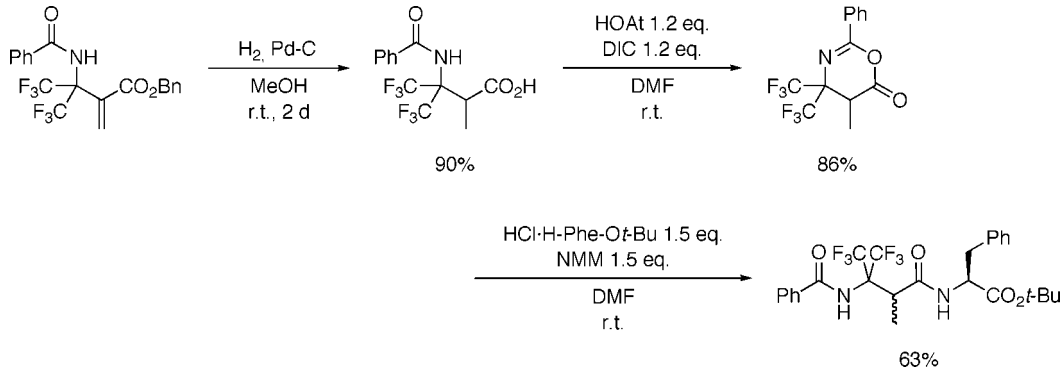
Type B β-aminocarbonyl compounds can also be prepared directly by reaction of methanolic ammonia with type A acetates.[108] In this transformation, nitrile derivatives cleanly afforded primary β-amino nitriles as their *Z* isomers, while ester derivatives gave a mixture of primary and secondary β-amino esters as their *Z* isomers by reaction of primary β-amino esters formed on the starting type A acetates (Scheme 31).

Nucleophilic displacement of type A Baylis−Hillman acetates with 2-formylimidazole gave either type A or type B adducts depending on the reaction conditions.[109] In the presence of DABCO, the reaction yielded type A adducts by double S_N2' reaction, whereas in the absence of DABCO, type B adducts were obtained (Scheme 32).

Scheme 65



Scheme 66



Yoon and co-workers carried out the displacement of type A Baylis−Hillman acetates with various amines in ethanol.[110] The reaction produced selectively type B β-aminocarbonyl compounds in high yields (Scheme 33). Esters and keto derivatives gave rise to *E* β-aminocarbonyl compounds, whereas nitrile derivatives yielded *Z* derivatives.

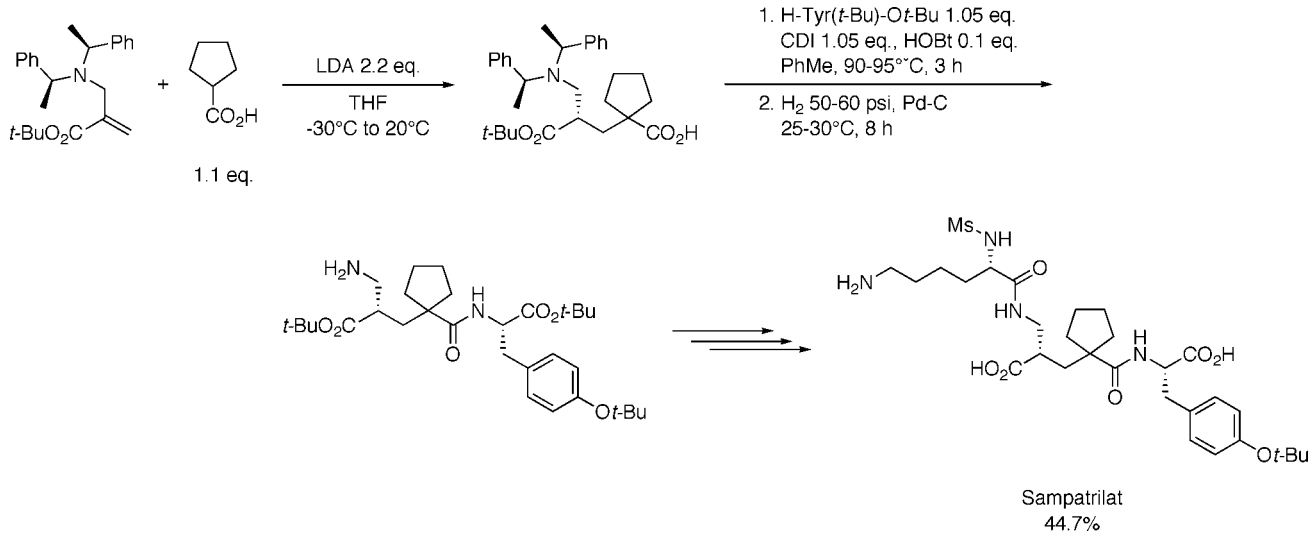
The hydroxyl group of Baylis−Hillman adducts can also be activated as a phosphate. Thus, Skowrońska and co-workers carried out the synthesis of cyclic β-amino esters by action of an amine or an azide on the corresponding phosphorylated derivatives (Scheme 34).[111] In this particular case, S_N2 and S_N2' lead to the formation of the same product.

4.1.4. Catalytic Allylic Amination of Baylis−Hillman Products

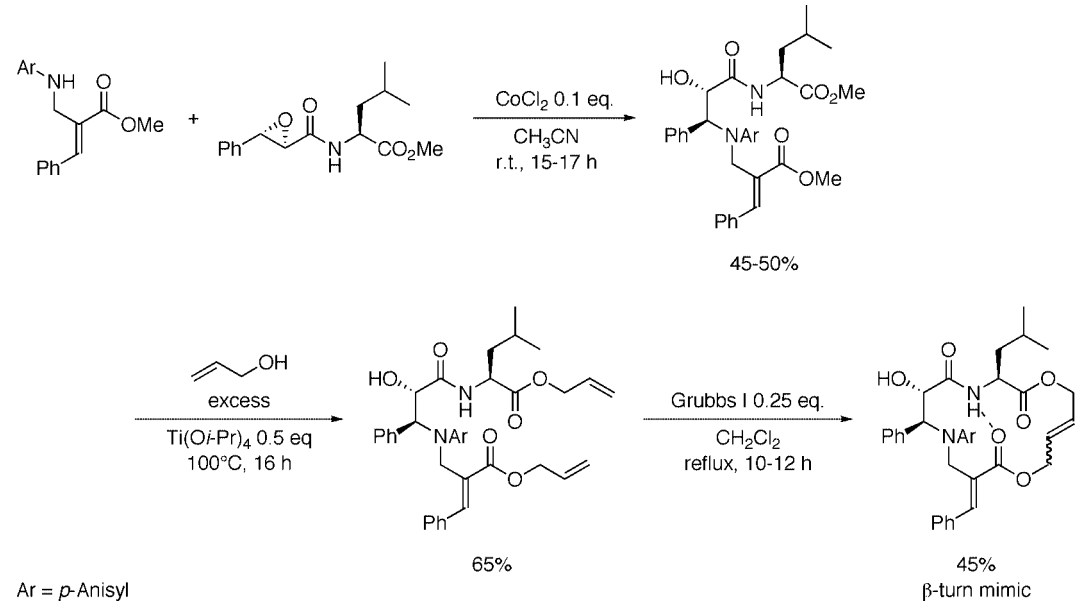
Orena and co-workers have developed a method allowing the formation of type A or B β-amino esters depending on the conditions used.[112,113] The β-hydroxy ester was first activated as a carbamate by the action of an isocyanate. The carbamate thus formed gave the type B β-amino ester by the action of DBU in a good yield, whereas in the presence of DABCO, it provided the type A β-amino ester by a double nucleophilic allylic substitution (Scheme 35).

This group has also shown that activation of type A β-hydroxy esters as acylcarbamates allowed the formation of type A β-amino esters by a similar treatment with DABCO (Scheme 36).[114]

Scheme 67



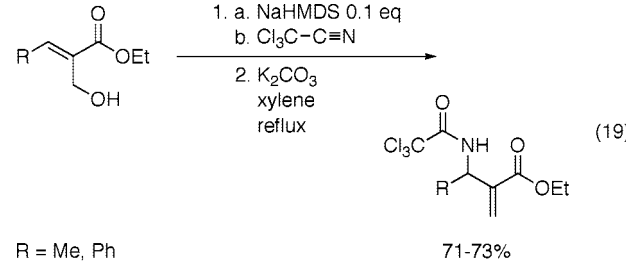
Scheme 68



Krische and co-workers showed that phosphines had the same effect as DABCO.[115] In this case, a double nucleophilic allylic substitution allowed the formation of type A β-amino esters substituted by various phthalimides (Scheme 37).

Activation of Baylis−Hillman alcohols as carbonates allows the same type of reaction.[116] Thus, treated by an amine in the presence of a catalytic quantity of DABCO, carbonates provided type A β-amino esters in good yields (eq 18).

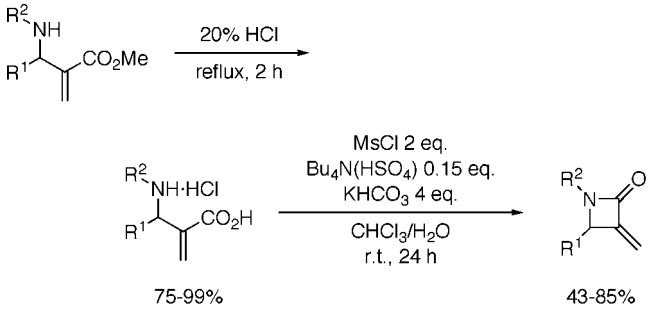
Orena and co-workers have also activated β-hydroxy esters as trichloracetimidates to carry out the synthesis of type A and B β-amino esters under similar conditions as those described previously (Scheme 38).[117−119] This method was also employed by the group of Ramachandran to carry out the synthesis of type A β-amino esters starting from type B β-hydroxy esters (eq 19).[120]



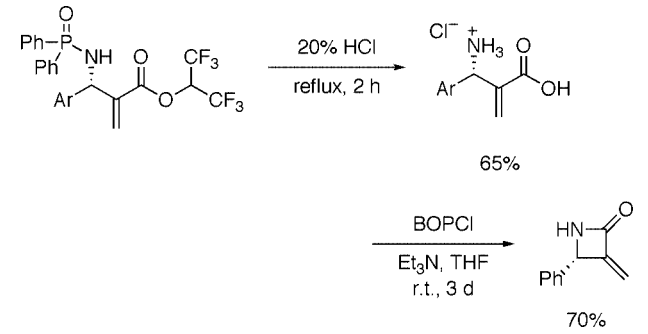
The group of Mamaghani developed another method to reach the type A or type B β-amino esters by activation of β-hydroxy esters as sulfamates with the Burgess reagent (Scheme 39).[121]

Using CAN as catalyst, Roy and co-workers were able to prepare a series of type B β-amino esters from type A acetates in high yields and with good selectivities in favor of the *E* isomer (Scheme 40).[122]

Scheme 69



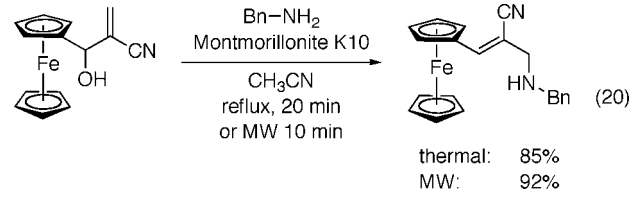
Scheme 70



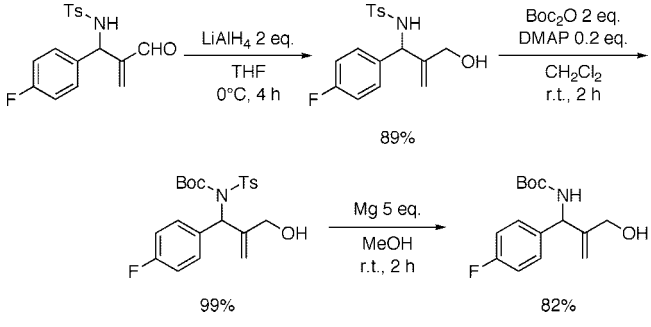
4.1.5. Activation of Baylis−Hillman Adduct under Heterogeneous Catalysis Conditions

Das and co-workers have recently described the synthesis of type B β-amino esters and β-amino nitriles from type A β-hydroxycarbonyl compounds using acetonitrile in the presence of Amberlyst-15 as heterogeneous catalyst (Scheme 41).[123]

Baylis−Hillman alcohols can also be activated by the use of Montmorillonite K10 clay. Using this catalyst, the group of Shanmugam prepared various trisubstituted alkenes by S_N2' displacement of the alcohols using various nucleophiles.[124] Among them, benzylamine gave the corresponding type B β-amino nitrile (eq 20).



Scheme 71



4.1.6. Asymmetric Allylic Amination

The group of Hamada has described the first stereoselective transformation of β-hydroxycarbonyl compounds into β-aminocarbonyl derivatives.[125] Cyclic Baylis−Hillman derivatives, activated as carbonates, were transformed under Pd-catalyzed conditions in the presence of DIAPHOX, a chiral diaminophosphine oxide ligand. The reaction proceeded with various amines to give the cyclic β-aminocarbonyl compounds in high yields and enantioselectivities (Scheme 42).

The enantioselective allylic substitution of type A Baylis−Hillman adducts can also take place in the presence of a chiral organocatalyst. Hou and co-workers have described the use of chiral paracyclophane monophosphines in the allylic susbstitution of Baylis−Hillman acetates and carbonates by phthalimide (Scheme 43).[126] In most cases, yields are good, but enantioselectivitites are moderate. Baylis−Hillman adducts derived from aliphatic aldehydes gave the lowest yields and enantiomeric excesses. Low enantiomeric excesses are also obtained in the case of Baylis−Hillman derivatives of methyl vinyl ketone.

4.2. Other Routes to Similar Products

4.2.1. Reaction of Enolates with in situ Generated Imines

Since imines derived from aliphatic aldehydes are difficult to prepare and isolate, Yamamoto and co-workers preferred to react an imine generated in situ with methyl *N*,*N*-dimethylaminopropanoate.[35,36] Permethylation of the amine followed by Hofmann elimination using DBU provided the corresponding β-amino ester (Scheme 44).

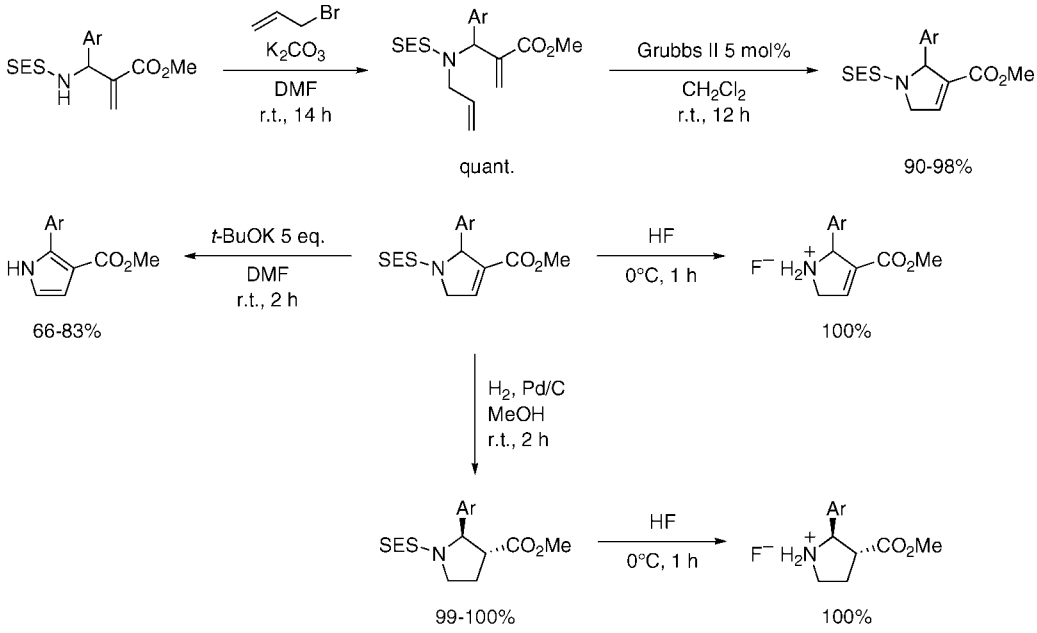
4.2.2. Reaction of α,β-Unsaturated Esters with Aminomethylbenzotriazoles

Katritzky and co-workers have described a two-step sequence allowing the preparation of β-amino esters.[127] Coupling of α,β-unsaturated esters with aminomethylbenzotriazoles under the influence of $TiCl_4$ provided β'-benzotriazolated β-amino esters via the in situ formation of an iminium ion. Elimination of the benzotriazole group upon treatment with NaH produced the *aza*-Baylis−Hillman adducts (Scheme 45).

4.2.3. Reaction of Vinylaluminums with Imines

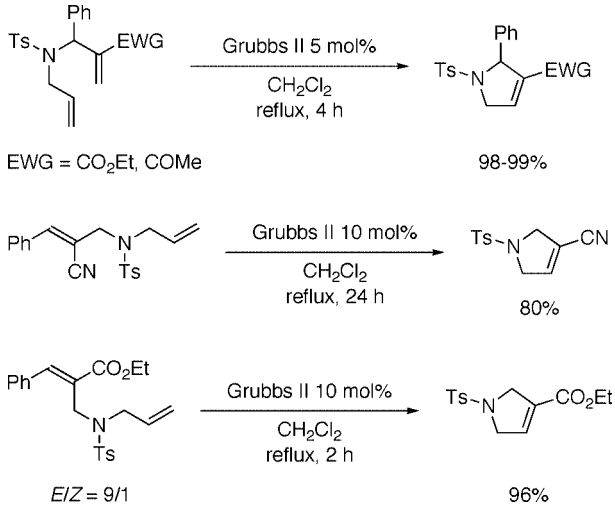
Greene and co-workers were the first to describe the reaction of vinylaluminiums with imines to prepare β-amino esters starting from chiral esters of propiolic acid (Scheme 46).[128]

Scheme 72

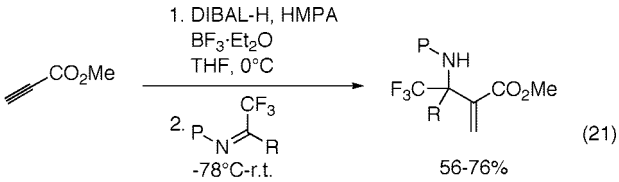


Ar = Ph, *m*-Tolyl, 3,5-Me_2-C_6H_3-, 2,3-(OCH_2O)-C_6H_3-, 3,5-$(MeO)_2$-C_6H_3-, 3-F-C_6H_4-, 4-Cl-C_6H_4-, 2-Br-C_6H_4-, 2-I-C_6H_4-, 4-MeO_2C-C_6H_4-, β-Np

Scheme 73



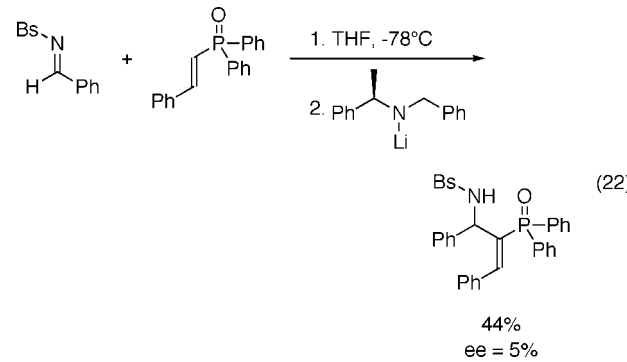
This procedure was also used by the group of Burger on imines derived from less reactive fluorinated ketones for which the Baylis−Hillman reaction does not give satisfactory results (eq 21).[129]



P = Bz, Boc
R = CF_3, CO_2Me

4.2.4. Reaction of Vinyllithiums with Imines

The group of Warren prepared a vinyllithium compound that, after reaction with imines, led to an *aza*-Baylis−Hillman adduct with poor selectivities (eq 22).[130]



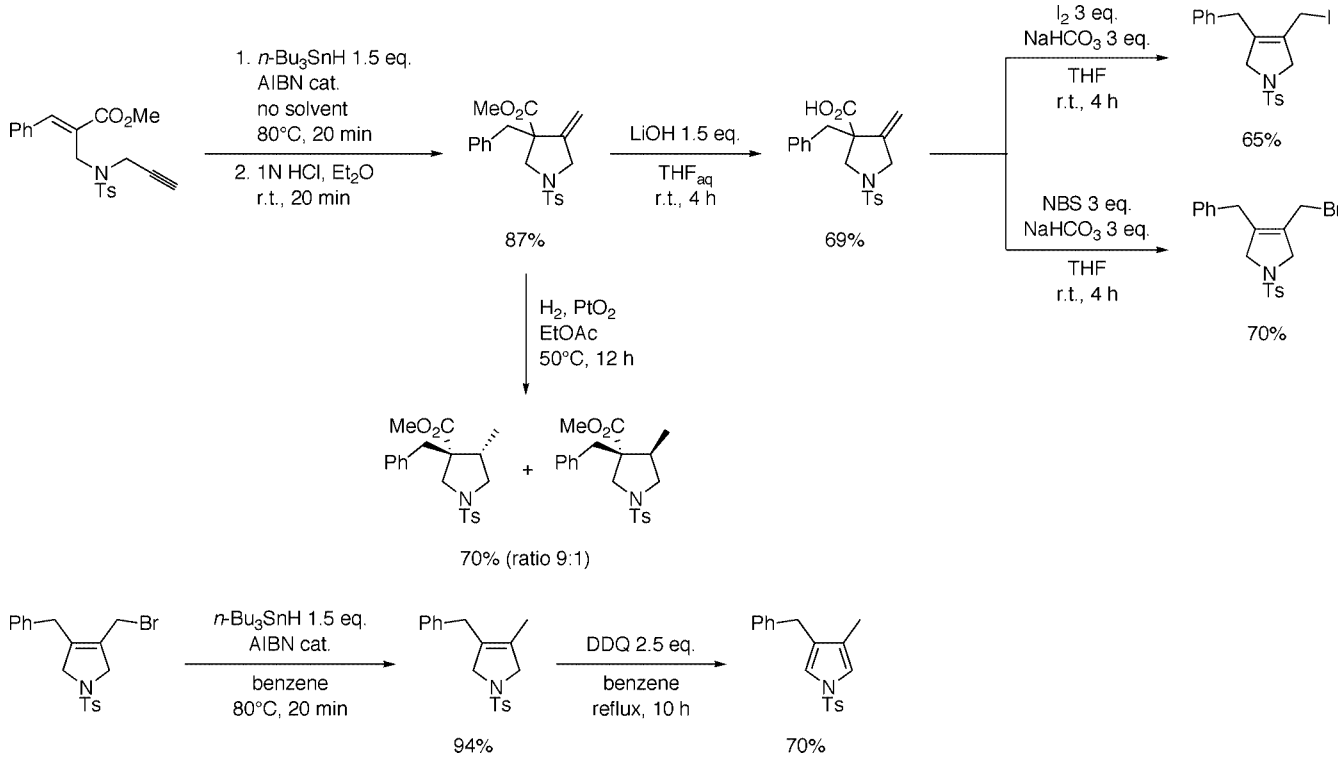
4.2.5. Reaction of in situ Generated 3-Iodo Allenoate

The group of Li has developed the synthesis of β-iodo *aza*-Baylis−Hillman adducts from acetylenic compounds and sulfonylimines or arylimines.[131,132] While the use of MgI_2 allows the formation of the *Z* isomer in the reaction of sulfonylimines,[131] the *E* compound could be obtained in the case of arylimines using TMS-I in the presence of $ZrCl_4$ as catalyst[132] (Scheme 47).

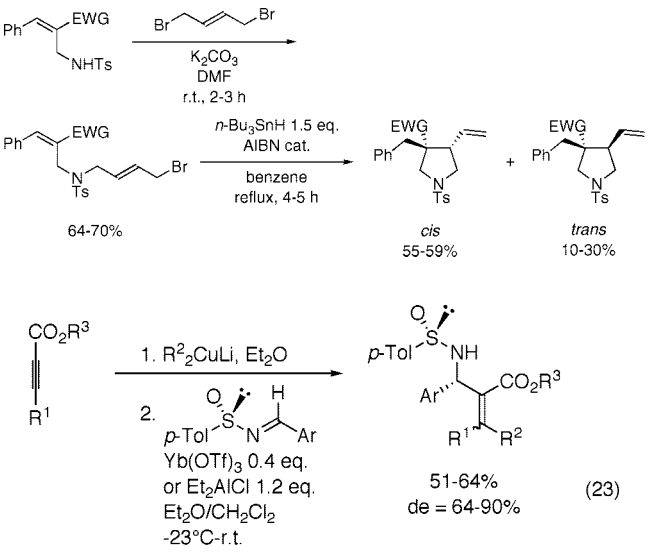
4.2.6. Reaction of Vinylcuprates with Imines

The group of Li carried out reactions between vinylcuprates and chiral sulfinylimines.[133−135] In contrast with the classical *aza*-Baylis−Hillman process, this method presents the advantage of allowing access to β-substituted amino derivatives (eq 23).

Scheme 74



Scheme 75



R^1 = Ph, Me, H
R^2 = Me, *n*-Bu, Ph
R^3 = Me, Et
Ar = Ph, 4-F-C_6H_4-, 4-Cl-C_6H_4-, 2-Furyl, 2-Thienyl

4.2.7. Amination of Activated Allylsilanes

Loreto and co-workers have developed an alternative route to *aza*-Baylis−Hillman adducts based on the aziridination of activated allylsilanes (Scheme 48).[136−138] Alkylation of tetraethylmethylenediphosphonate, diethyl β-ketophosphonates, or ethyl 2-(diethoxyphosphoryl)acetate with iodomethyltrimethylsilane followed by a Wittig−Horner reaction produced an activated allylsilane in moderate-to-good yields. Aziridination of the allylsilane using ethyl nosyloxycarbamate in the presence of CaO followed by acid-mediated elimination of the silyl group and ring-opening of the aziridine produced the β-amino derivatives in moderate yields.

This reaction can also take place with cyclohexylidene derivatives to produce β,β-disubstituted β-amino esters in moderate yields (Scheme 49).[139]

4.2.8. Addition of Activated Methylene Followed by Horner−Wadsworth−Emmons Olefination

Gadja and co-workers developed a novel access to β-amino phosphonates by a two-step sequence.[140] Addition of tetraethylmethylenediphosphonate on in situ generated Boc-imines gave the corresponding addition products in excellent yields. These substituted methylenediphosphonates were then submitted to a Horner−Wadsworth−Emmons olefination with formaldehyde to produce the *aza*-Baylis−Hillman adducts in high yields (Scheme 50).

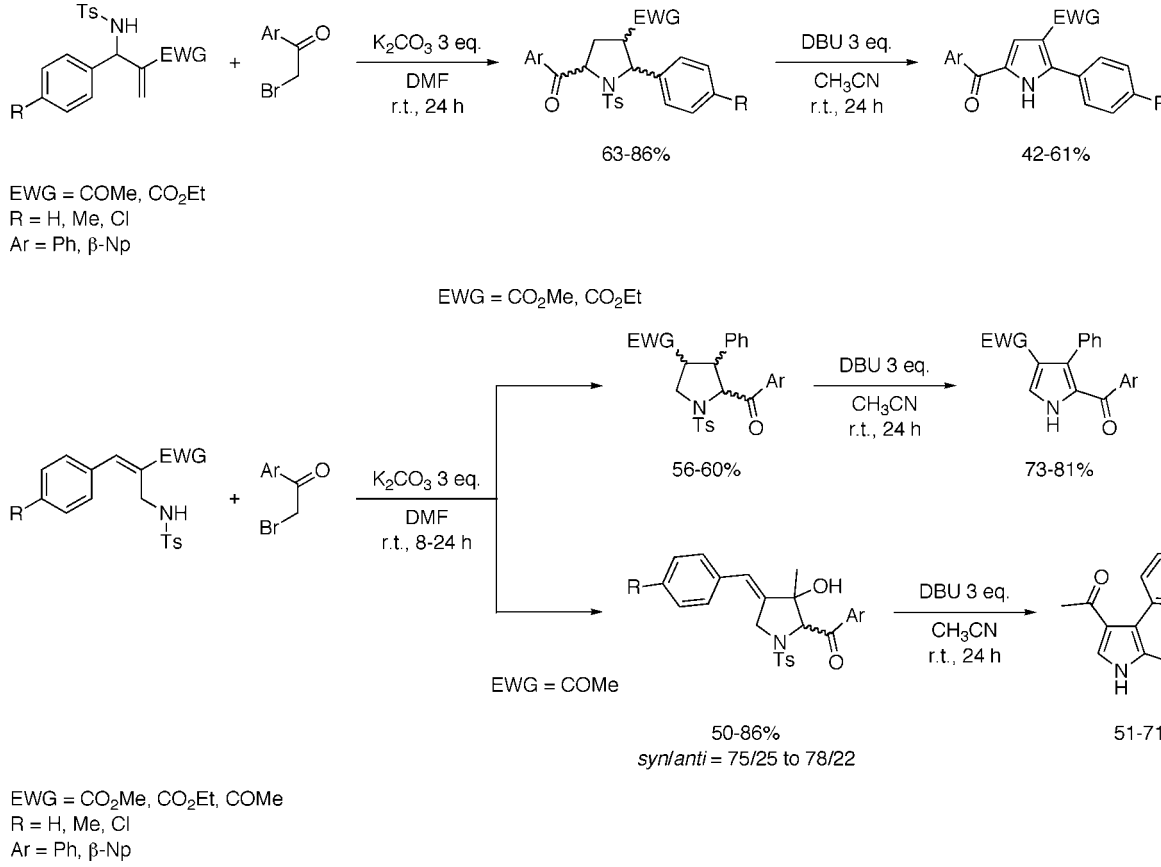
4.2.9. Tandem Thio-Michael/Nucleophilic Addition of Thiolate

The group of Kamimura has recently developed an alternative asymmetric access to β-amino esters.[141] A sequential thio-Michael/nucleophilic addition of magnesium thiolate with *t*-butyl acrylate and chiral *p*-toluenesulfinylimines followed by an oxidation/thermal elimination of the resulting sulfoxide allowed the preparation of β-amino esters in high yields and diastereoselectivities (Scheme 51).

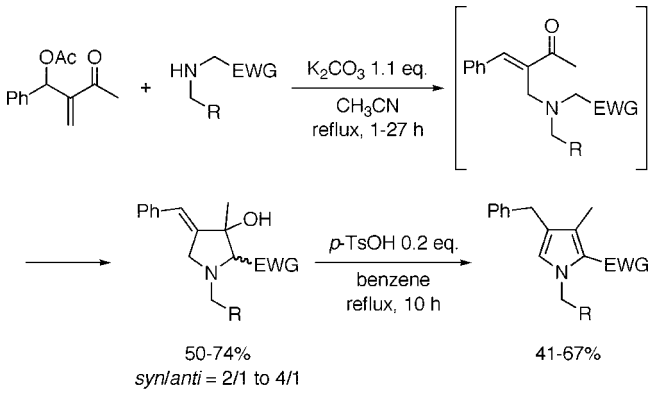
4.2.10. Tandem Mannich Reaction/Isomerization

Recently, Barbas and co-workers have described an alternative asymmetric synthesis of β-amino aldehydes by a tandem asymmetric Mannich reaction/isomerization.[142] The isomerization was catalyzed by imidazole (Scheme 52).

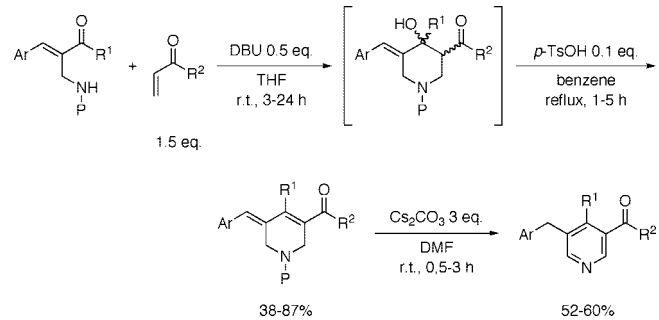
Scheme 76



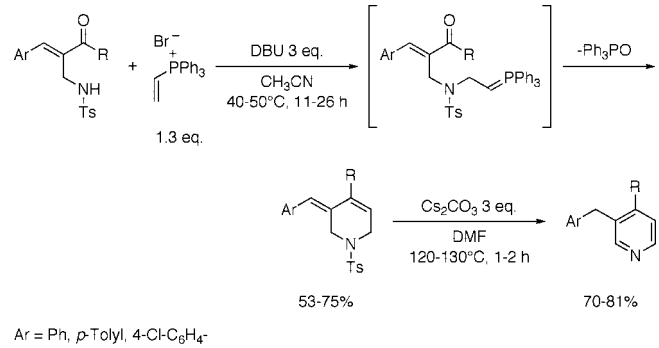
Scheme 77



Scheme 78



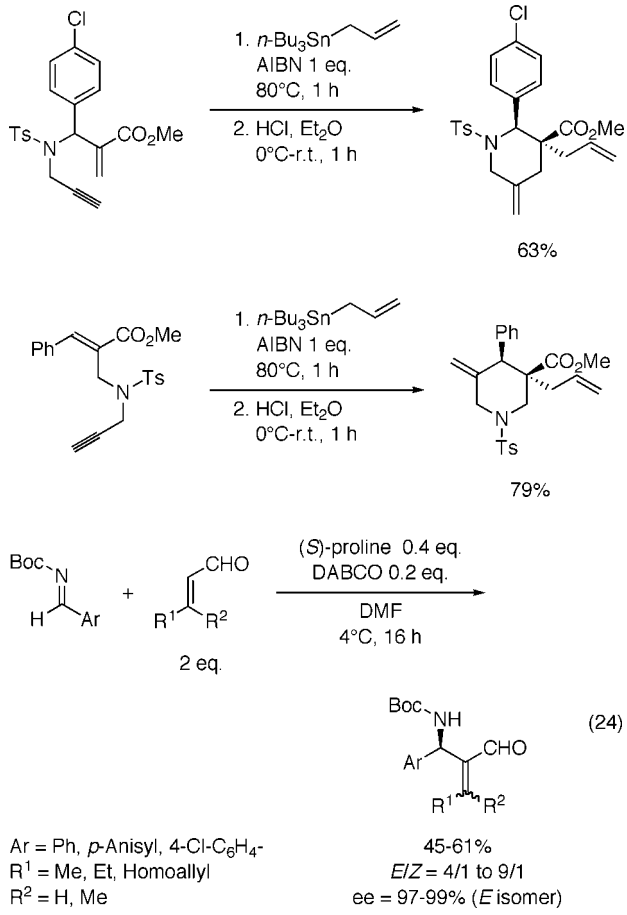
Scheme 79



Products were formed in moderate yields but with high diastereoselectivities, as a mixture of *E* and *Z* isomers. The *E*/*Z* ratio could be increased in favor of the *E* isomer by treatment of the mixture with an excess of imidazole without epimerization.

This process was also used by the group of Córdova in the reaction of Boc-imines with enals (eq 24).[143] Again, products were obtained in moderate yields and high diasteroselectivities as a mixture of *E* and *Z* isomers.

Scheme 80



β,γ-Unsaturated esters were also used as a source of β-substituted β-amino esters. Shibasaki and co-workers described a direct Mannich reaction of β,γ-unsaturated esters with diphenylphosphinoylimines catalyzed by Ba(O*p*-Anisyl)$_2$ followed by an isomerization process (Scheme 53).[144] The reaction proceeded in good yields, except in the case of some imines derived from aliphatic aldehydes. The reaction is also highly regioselective; the isomerized adducts were obtained as the major compounds, but lower α/γ regioselectivities were observed for imines derived from aromatic aldehydes bearing electron-withdrawing groups. The use of tosylimines and Boc-imines in this reaction was also investigated. If tosylimines did not give any adduct, Boc-imines gave mixtures of α- and isomerized adducts in low yields. Chiral ligands have also been used in this process. The use of a (*S*)-biaryldiol allowed the formation of the *aza*-Baylis−Hillman adducts with good enantioselectivities (Scheme 54).

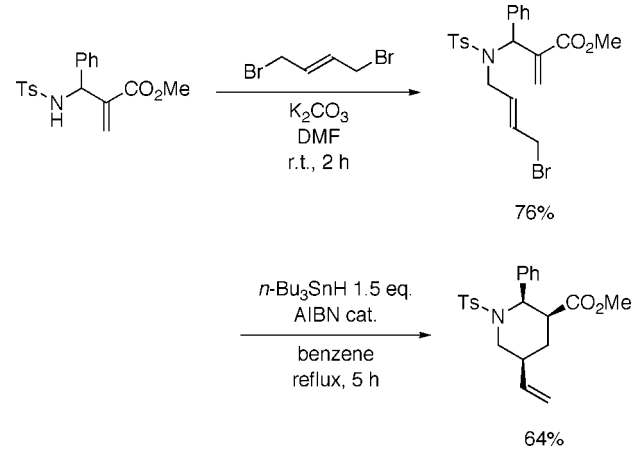
5. Use of aza-Baylis−Hillman Adducts in Synthesis

The *aza*-Baylis−Hillman reaction and related transformations provide efficiently highly functionalized synthons. Recently, further transformations of the *aza*-Baylis−Hillman adducts has provided straightforward access to a wide variety of organic molecules.

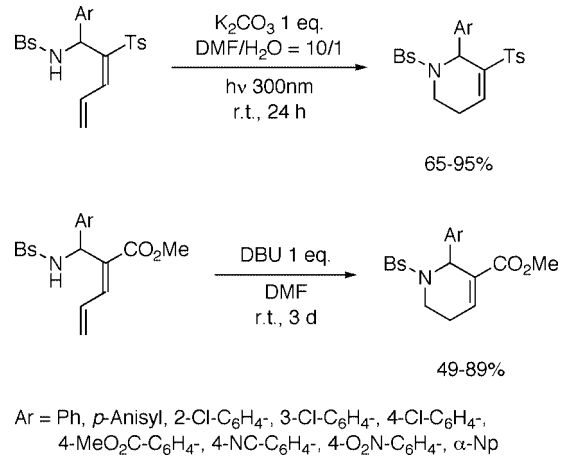
5.1. Synthesis of Cinnamic Acid Derivatives

Kim and co-workers have carried out the synthesis of cinnamic acid derivatives by Friedel−Crafts reactions on

Scheme 81



Scheme 82



β-amino esters and β-amino nitriles in the presence of sulfuric acid.[145] In this reaction, β-amino esters gave derivatives presenting an *E* configuration, whereas β-amino nitriles gave *Z* derivatives (Scheme 55).

5.2. Synthesis of Amino Acid Analogues and Applications in Peptide Synthesis

5.2.1. Synthesis of Linear β-Amino Esters

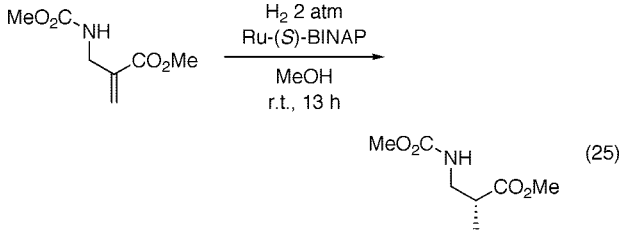
Kim and co-workers have developed a stereoselective method for the conversion of type A β-amino esters into type B β-amino esters using *N*,*N*-dimethylformamide dimethylacetal (DMF−DMA), based on the leaving group character of the tosylamino group.[146] The configuration of the product depends on the nature of the starting substrate: β-amino esters gave allylic amines with *E* configuration, whereas β-amino nitriles gave products with *Z* configuration (Scheme 56).

The same compounds can be obtained by reaction of *aza*-Baylis−Hillman products with *N*-methyltosylamine in the presence of K_2CO_3.[146] Reaction of β-amino nitrile gave exclusively the product with *Z* configuration. The reaction with β-amino ester was less selective, but *E* compound was still favored (Scheme 57).

Hydrogenation of type B β-amino esters have been investigated by several research groups. Brown and co-workers have studied the hydrogenation of *N*-Boc and *N*-acetyl-α-methylene-β-amino esters.[91] The reaction was conducted in the presence of a chiral phosphine and resulted

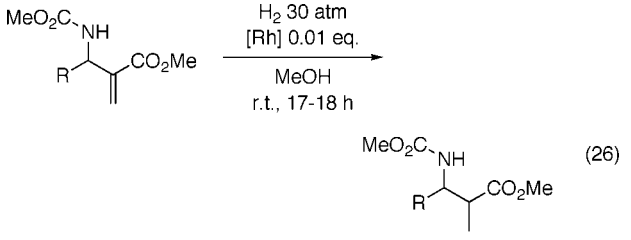
in the kinetic resolution of the starting material, recovered with high enantiomeric excess (Table 20).

Yamamoto and co-workers have studied the enantioselective hydrogenation of methyl α-(methoxycarbonylaminomethyl)acrylate using various rhodium and ruthenium complexes derived from chiral phosphines.[36] When performed in the presence of Ru-(*S*)-BINAP, hydrogenation gave the *R* product with 85% ee (eq 25). They have also studied the diastereoselective hydrogenation of α-methylene *β*-amino esters using various ruthenium and rhodium complexes catalysts.[35,36] The best results were obtained using the $[Rh(cod)(dppb)]^+ClO_4^-$ complex (eq 26). Results are generally good except in the case of sterically hindered molecules bearing a *t*-butyl as an R group, for which both conversion and selectivity are poor.



(25)

τ = 100%
ee = 85%

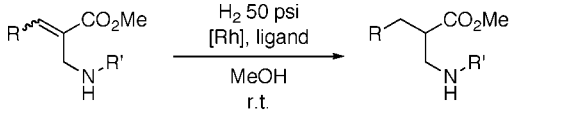


(26)

[Rh] = $Rh[(cod)(dppb)]^+ClO_4^-$
R = Ph, Me, *i*-Pr, *i*-Bu, *t*-Bu

τ = 53-100%
anti/*syn* = 23/77 to 97/3

Chan and co-workers have studied the enantioselective hydrogenation of α-aminomethylacrylates containing a free N−H group in the presence of various chiral phosphine ligands (eq 27).[147] Hydrogenation occurred with a high level of enantioselectivity for numerous ligands, but the best results were obtained in the case of hydroxylamine derivatives. Formylation of the amino group slowed down the reaction and resulted in the loss of enantioselectivity.



(27)

94-98%
ee = 85->99.5%

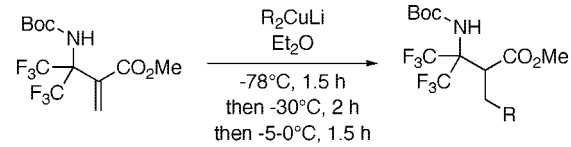
R = Ph, *n*-Pr
R' = Bn, BnO-

Enantioselective hydrogenation of *β*-phthalimidomethylacrylates occurred efficiently in the presence of various phosphine ligands (Scheme 58). The use of a mannitol-derived phosphine ligand produced the reduced *β*-amino esters in good yields and high enantioselectivities except for compounds bearing an heteroaromatic or aliphatic group on the double bond.[148] These results were further improved by the use of a BoPhoz-type ligand, which provided both high yields and enantioselectivities.[149]

Lamaty and co-workers have performed the hydrogenation of PEG-supported *β*-amino esters in the presence of Wilkinson's catalyst to produce the reduced compounds with excellent conversions (Scheme 59).[42]

The group of Jacobsen has recently described various transformations of Ns-protected α-methylene-*β*-amino esters for the formation of new *β*-amino esters.[14] Transformations included hydrogenation, dihydroxylation, epoxidation, [3+2]-cycloaddition of aldoxime, and conjugate addition of 1,3-dicarbonyl compounds and cyanide (Scheme 60).

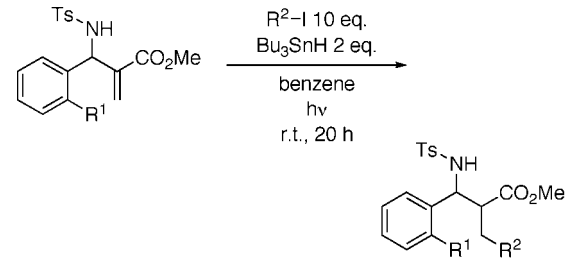
Hydrogenation of α-methylene-*β*-amino esters have also been reported by the group of Burger and have been used in the synthesis of peptides (see section 5.2.3).[55] This group has also described the addition of cuprates on the double bond (eq 28).



(28)

R = Me 73%
R = Ph 65%

Kündig and co-workers have described the synthesis of *β*[2,3]-amino esters by radical addition on α-methylene-*β*-amino esters.[150] The reaction proceeded with various alkyl iodides in good yields and with moderate-to-good diastereoselectivities (eq 29).



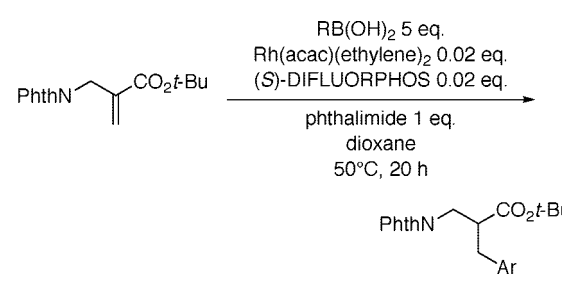
(29)

R^1 = H, OMe, Me, Cl, F
R^2 = Et, *i*-Am, CyHx, *t*-Bu

84-97%
syn/*anti* = 1.1/1 to 12/1

β[2]-Amino esters were also prepared by the group of Roumestant by radical addition and Heck reaction on a bis-Boc α-methylene-*β*-amino ester (Scheme 61).[151]

The group of Sibi was interested in the synthesis of *β*[2]-amino esters by rhodium-catalyzed conjugate addition of arylboronic acid on suitably protected α-methylene-*β*-amino esters.[152] The reaction was carried out on phthalimide-protected derivatives, and good enantiomeric excesses were obtained when DIFLUORPHOS was used as chiral ligand (eq 30).



(30)

Ar = Ph, *p*-Tolyl, *p*-Anisyl, 4-Cl-C_6H_4-, 3,5-$(CF_3)_2$-C_6H_3-, β-Np

16-95%
ee = 63-91%

Jung and co-workers have described the *N*-functionalization of type B β-amino esters supported on a chlorotrityl resin.[153] Transformations included acylation, alkylation, and sulfonation followed by cleavage from the resin (Scheme 62).

5.2.2. Synthesis of Amino Acid Analogues

Orena and co-workers have carried out the synthesis of phenylisoserine analogues.[113,117] The strategy implied a selective iodocyclization of *N*-benzoyl-β-amino esters; the dihydro-1,3-oxazoles thus prepared were the key synthon to obtain analogues of phenylisoserine (Scheme 63). The method presents the advantage of allowing the synthesis of both *cis*- and *trans*-diastereoisomers by carrying out an inversion of configuration of one of the asymmetric centers of the dihydro-1,3-oxazole (Scheme 64).

This group has also carried out the synthesis of constrained analogues of β-homoserine and aspartic acid.[114] The strategy is based on the use of an *aza*-Baylis−Hillman adduct derived from ethyl glyoxylate. This product has two reaction centers: the conjugated double bond and the ester function. A suitable amine, here the (*S*)-methylbenzylamine, reacts with the *aza*-Baylis−Hillman adduct to form pyrrolidin-2-ones. Functional transformations such as replacement of the trichloromethylcarbamate protection by a Boc, reduction of the ester function, and deprotection of the pyrrolidinic nitrogen provided constrained analogues of β-homoserine and aspartic acid (Scheme 65).

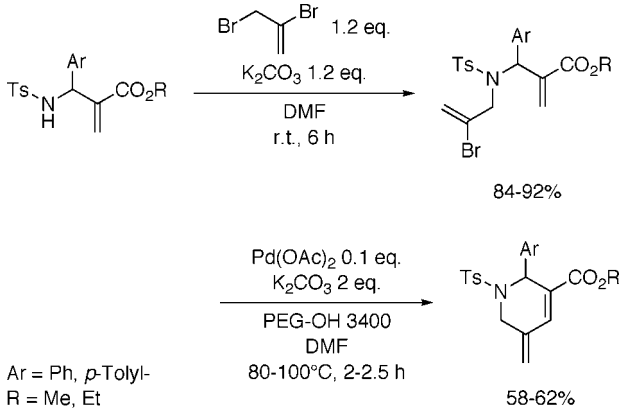
5.2.3. Application in Peptide Synthesis

Burger and co-workers have coupled reduced β-amino acids with α-amino esters.[55] Direct coupling of the β-amino acid gave the dipeptide in poor yield. They discovered that the coupling proceeds via the formation of an 1,3-oxazin-6-one intermediate. Stepwise formation of this intermediate followed by the reaction with α-amino ester afforded the dipeptide in good yield (Scheme 66).

The Pfizer company has described a route to Sampatrilat using Baylis−Hillman chemistry.[154] A chiral α-methylene-β-amino ester is subjected to a Michael addition of cyclopentanecarboxylic acid. The glutarate derivative thus obtained was coupled with suitably protected tyrosine (Scheme 67). Deprotection of the amine followed by several transformations led to Sampatrilat.

Iqbal and co-workers have used type B β-amino esters for the synthesis of a constrained β-turn mimic using the turn-inducer character of α-dehydro-β-amino esters (Scheme 68).[105]

Scheme 83



5.3. Synthesis of β-Lactams

Hoffmann and co-workers have described the synthesis of β-lactams from both type A and B β-amino acids under phase-transfer catalysis conditions (Scheme 69).[92]

The group of Hatakeyama has carried out the synthesis of β-lactams in two steps starting from protected β-amino esters: a deprotection step followed by a cyclization step using BOPCl in the presence of triethylamine (Scheme 70).[76]

5.4. Synthesis of Amino Alcohols

β-Amino aldehydes can be easily reduced into β-amino alcohols by the use of $LiAlH_4$.[25] Moreover, the group of Shi has shown that the tosyl group can be advantageously replaced by a Boc group. The Boc protection can be removed under milder conditions than the tosyl group and, therefore, is more compatible with elaborated molecules bearing many functional groups (Scheme 71).

5.5. Synthesis of Pyrrolidines, Pyrrolines, and Pyrroles

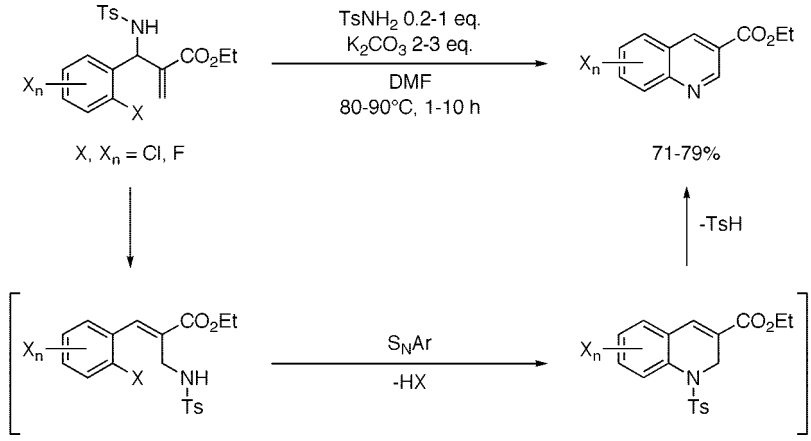
Lamaty and co-workers have described the synthesis of SES-protected pyrrolines using ring-closing metathesis as a key step (Scheme 72).[19] These SES-protected pyrrolines allowed the access to free pyrrolines, and free pyrroles depending on the deprotection conditions used. Under basic conditions using *t*-BuOK, a dehydrodesulfinylation of the SES group led to the formation of pyrroles in good yields.[19] Performed in neat HF, deprotection allows the formation of the free pyrrolines as hydrofluoride salts. A simple hydrogenation of the SES−pyrrolines afforded the corresponding *trans*-SES-pyrrolidines with high diastereoselectivities and free pyrrolidines after HF deprotection (Scheme 72).[155] A similar approach to the synthesis of pyrrolines by ring-closing metathesis from Ts-protected β-amino esters has been described by Adolfsson and co-workers.[156]

Kim and co-workers have also described a RCM approach to Ts-protected pyrrolines from *N*-allyl type A and B β-aminocarbonyl compounds obtained by displacement of Baylis−Hillman acetates using Ts-allylamine.[157] RCM of type A compounds gave 2,3-disubstituted Ts-pyrrolines, while type B compounds gave 3-substituted Ts-pyrrolines (Scheme 73). Later, this group studied the hydrogenation of these pyrrolines, which produced the corresponding *cis*-2,3-disubstituted Ts-pyrrolidines.[158] This result may not be in agreement with the observations of Lamaty and co-workers.[155] A careful examination of the spectral data, especially the value of the coupling constants, seems to point out that the *trans*-diastereoisomers (the same as the ones obtained by the group of Lamaty unambiguously determined to be *trans* by X-ray analysis) were actually obtained.

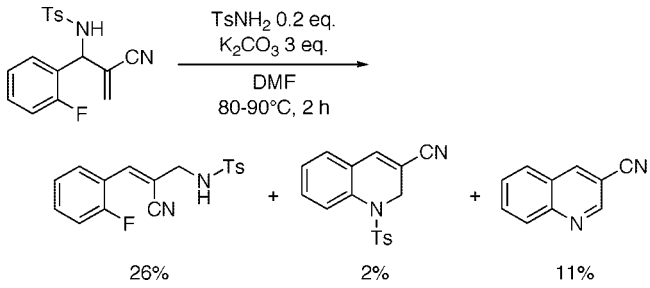
The group of Kim has carried out the synthesis of pyrrolines and pyrroles by radical cyclization of type B β-amino esters (Scheme 74).[159] Hydrogenation of the 3,4,4-trisubstituted pyrroline occurred in the presence of PtO_2 to provide the reduced compound with a high diastereoselectivity in favor of the *cis*-diastereoisomer.[158]

Under similar radical conditions, type B β-amino esters or nitriles bearing an (*E*)-4-bromobut-2-enyl chain cyclized via the formation of an allyl radical to produce 3,3-disubstituted-4-vinylpyrrolidine derivatives in moderate yields (Scheme 75). The formation of the *cis*-diastereoisomer as the major compound was attributed to unfavorable steric

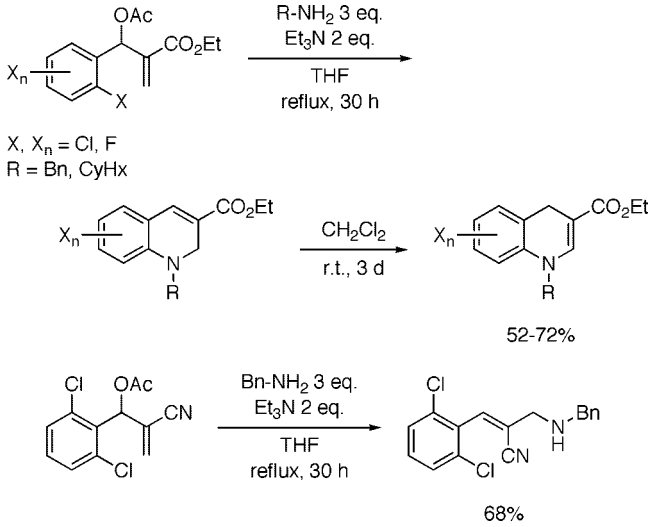
Scheme 84



Scheme 85



Scheme 86



hindrance in the transition state leading to the anti diastereoisomer.[160]

Kim and co-workers have recently described the synthesis of polysubstituted pyrroles from type A and B β-aminocarbonyl compounds (Scheme 76).[161] *N*-alkylation using a bromomethyl ketone followed by intramolecular Michael addition gave Ts-protected polysubstituted pyrrolidines, which upon treatment with DBU yielded substituted pyrroles by dehydrodesulfinylation/aromatization in moderate-to-good yields. It should be noted that, in the case of type B β-amino ketones, alkylation is followed by an aldol condensation, which gave hydroxypyrrolidines. Treated by DBU, the latter are converted into polysubstituted pyrroles by retro-aldol condensation followed by intramolecular Michael addition and dehydrodesulfinylation/aromatization.

Similar pyrroles were obtained by S_N2' displacement of type A acetates with an appropriate amine followed by intramolecular aldol condensation under basic conditions. Finally, an acid-catalyzed dehydration with concomitant double bond isomerization produced 1,2,3,4-tetrasubstituted pyrroles (Scheme 77).[162]

5.6. Synthesis of Piperidines, Tetrahydropyridines, and Pyridines

Kim and co-workers carried out the synthesis of pyridines starting from type B β-amino ketones.[104] The strategy implied a conjugate addition of the β-amino ketone on a vinylic ketone or an acrylate followed by an aldol condensation in the presence of DBU. Finally, a dehydration reaction in the presence of *p*-toluenesulfonic acid, followed by a dehydrodesulfinylation reaction accompanied with an aromatization, provided 3,4,5-trisubstituted pyridines (Scheme 78).

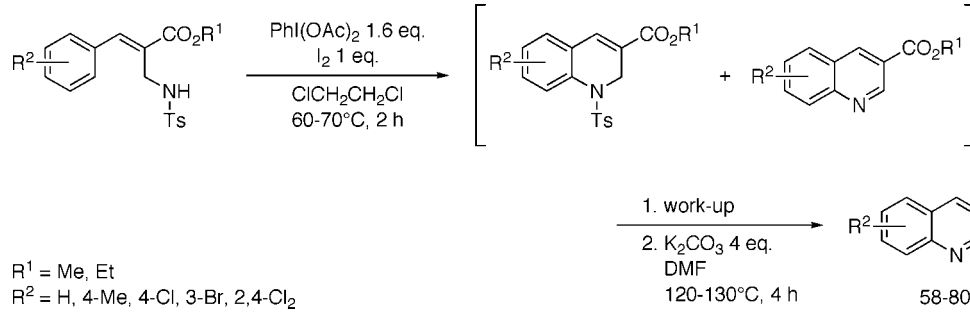
Another strategy consisted of using the Schweizer reaction.[163] A Michael addition of β-amino ketones on vinyltriphenylphosphonium bromide followed by an intramolecular Wittig reaction gave tetrahydropyridines. A final dehydrodesulfinylation reaction provided the pyridines (Scheme 79).

The group of Kim has recently described a radical cyclization approach to the synthesis of piperidines.[164] Allylstannane-mediated radical cyclization of enynes derived from type A and B β-amino esters afforded the corresponding 5-methylenepiperidines in good yields (Scheme 80).

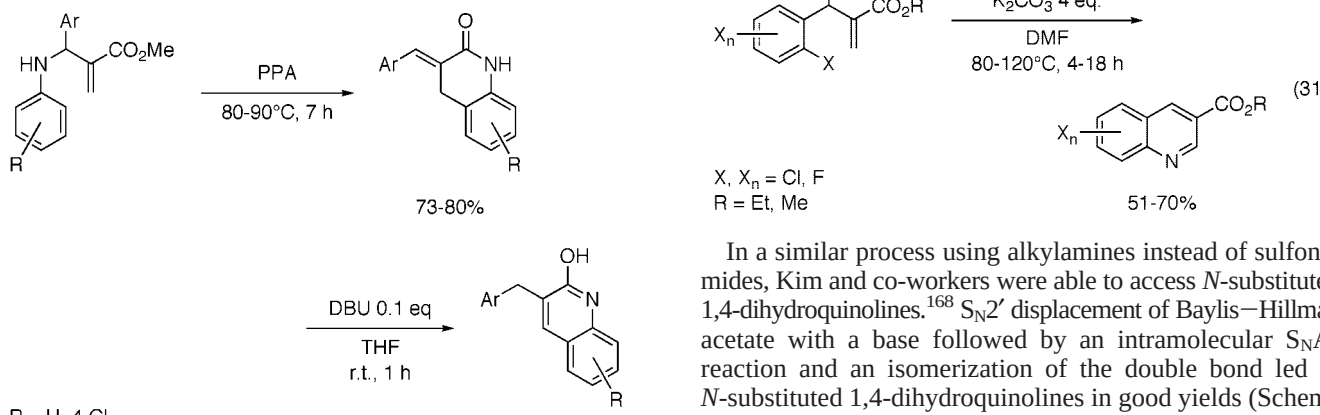
In contrast with type B β-amino esters (see section 5.5), type A β-amino esters bearing an (*E*)-4-bromobut-2-enyl chain cyclized via the formation of an allyl radical to produce *cis*-2,3-disubstituted-5-vinylpiperidine derivatives in good yields (Scheme 81).[160]

Back and co-workers have described the synthesis of tetrahydropyridines from β-amino esters obtained by a vinylogous *aza*-Baylis−Hillman reaction (see section 2.2.5).[45,46] Cyclization of these compounds occurred by intramolecular conjugate addition to the terminal position of the diene using K_2CO_3 in a mixture of DMF and water (10/1). Under these conditions, only the *E* isomer cyclized; the *Z* isomer could not adopt a conformation compatible with the 6-centered transition state required for the cyclization. Upon irradiation with UV light at 300 nm, the *Z* isomer can isomerize into the *E* isomer. Thus, subjecting a mixture of *E* and *Z* isomers to the cyclization

Scheme 87



Scheme 88



conditions under UV irradiation gave the tetrahydropyridines in high yields. Methyl pentadienoate derived products cyclized using DBU in DMF. Cyclization of the *E* isomer gave the tetrahydropyridines in good yields (Scheme 82).

Tetrahydropyridines were also obtained by an intramolecular Heck reaction from suitably substituted β-amino esters using a mixture of PEG and DMF as solvent (Scheme 83).[165] However, converting these tetrahydropyridines into pyridines resulted in extensive decomposition, and pyridines were formed in low yields.

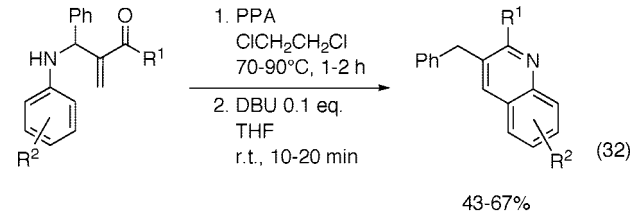
5.7. Synthesis of Quinolines and Dihydroquinolines

The group of Kim has carried out the synthesis of quinolines starting from *N*-tosyl-β-amino esters.[166] This "one-pot" reaction implied the in situ formation of type B *N*-tosyl-β-amino ester followed by an aromatic nucleophilic substitution and a dehydrodesulfinylation of the tosyl group to provide the quinoline (Scheme 84). The same quinolines can be obtained starting from acetates of Baylis−Hillman adducts in a similar way, but the reaction required at least a stoichiometric amount of Ts-NH_2 (eq 31).[167] When the reaction was carried out on *N*-tosyl-β-amino nitriles, the reaction gave a mixture of type B β-amino nitrile, dihydroquinoline, and quinoline (Scheme 85).[166]

In a similar process using alkylamines instead of sulfonamides, Kim and co-workers were able to access *N*-substituted 1,4-dihydroquinolines.[168] S_N2' displacement of Baylis−Hillman acetate with a base followed by an intramolecular S_NAr reaction and an isomerization of the double bond led to *N*-substituted 1,4-dihydroquinolines in good yields (Scheme 86). In the case of nitrile compound, S_N2' displacement of the acetate led to the formation of a product presenting a *Z* configuration that is not able to cyclize.

This group has also developed another access to these types of quinolines substituted by an ester group.[103] The reaction consisted of an oxidative cyclization of the tosylamidyle radical generated by treatment of type B β-amino esters with iodobenzene diacetate and iodine (Scheme 87).

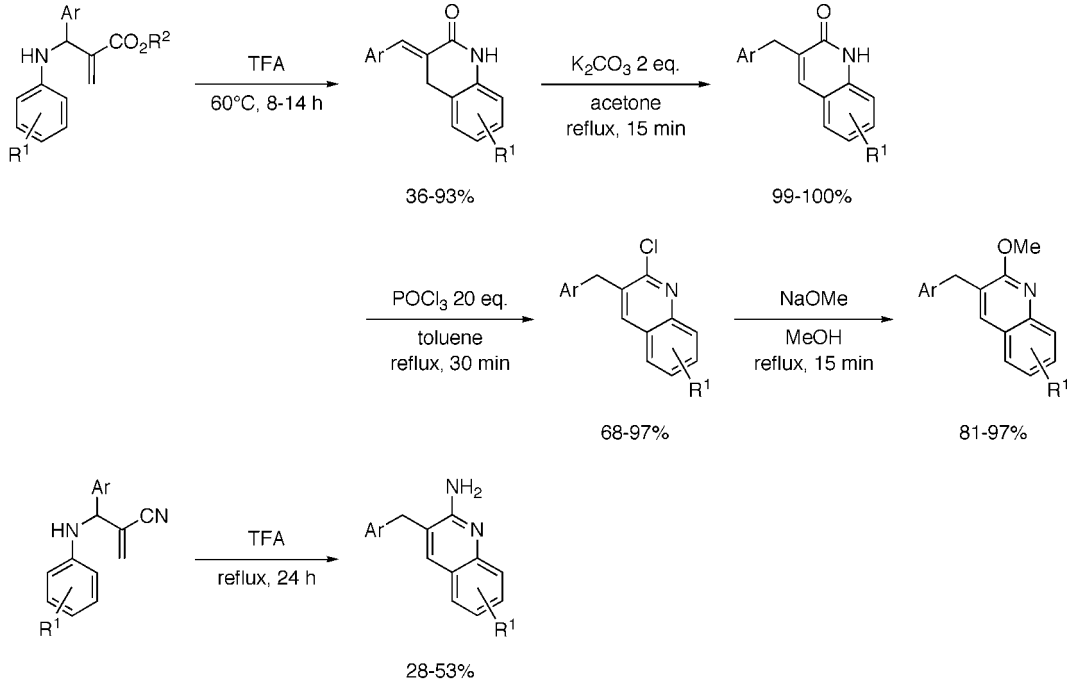
Kim and co-workers have investigated the reactivity of *N*-aryl β-aminocarbonyl compounds in polyphosphoric acid. In the presence of PPA, *N*-aryl β-amino esters underwent a Claisen rearrangement followed by a condensation, leading to the formation of quinolones in good yields.[169] Subsequent double bond isomerization followed by tautomerization gave quinolinols in high yields (Scheme 88). In the same manner, treatment of *N*-aryl β-amino ketones with PPA led to the formation of polysubstituted quinolines (eq 32).[170]



This Claisen rearrangement can also take place in the presence of trifluoroacetic acid.[171] In these conditions, Pathak and co-workers were able to use a larger variety of aniline derivatives to form 2-methoxyquinolines. The method was extended to nitrile derivatives to produce 2-aminoquinolines (Scheme 89).

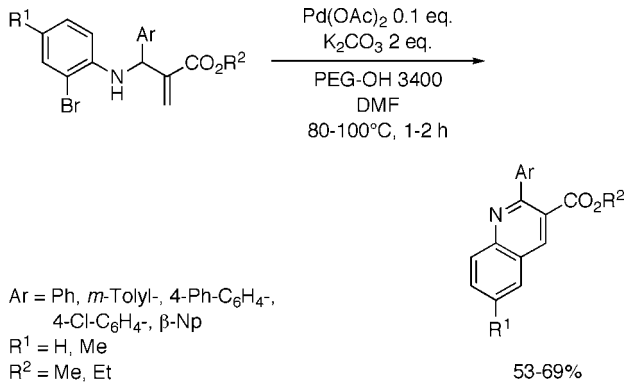
The group of Kim has shown that β-amino esters derived from *o*-nitrobenzaldehyde react in trifluoroacetic acid in the

Scheme 89



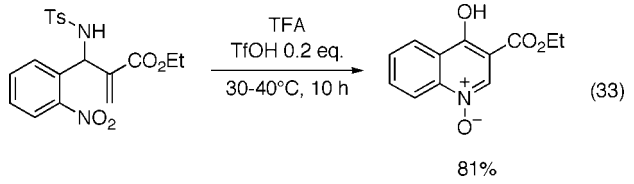
R^1 = H, 2-Me, 4-Me, 4-MeO, 3,4,5-$(MeO)_3$, 4-F, 4-Cl, 4-Br
R^2 = Me, Et, *t*-Bu
Ar = Ph, 2-F-C_6H_4-, 2-Cl-C_6H_4-, 4-Br-C_6H_4-, 2,4-Cl_2-C_6H_3-, 2-Pyridyl

Scheme 90



Ar = Ph, *m*-Tolyl-, 4-Ph-C_6H_4-, 4-Cl-C_6H_4-, β-Np
R^1 = H, Me
R^2 = Me, Et

presence of triflic acid to provide 4-hydroxyquinoline *N*-oxide, with the tosylamide group acting as a leaving group (eq 33).[172]



(33)

2-Arylquinolines were prepared by an intramolecular Heck reaction of *N*-aryl β-amino esters followed by aerobic oxidation (Scheme 90).[165] The reaction was performed using a mixture of PEG and DMF as solvent and produced 2-arylquinolines in moderate yields.

5.8. Synthesis of Pyrroloquinolines

The group of Lamaty described the synthesis of diverse pyrroloquinolines derived from a pivotal chloroquinoline obtained by the RCM/aromatization strategy (see section 5.5) starting from the *aza*-Baylis−Hillman adduct of 2-nitrobenzaldehyde and methyl acrylate (Scheme 91).[173] The key step, after the hydrogenation of the nitro group, is the cyclization of a pyrrolo amino ester to form a lactam, which gives by chlorination the corresponding imidoyl chloride. Diverse amine- and aryl-substituted pyrroloquinolines were obtained by the coupling of the chloride intermediate either directly with an amine or with a boronic acid under palladium-catalysis conditions. It has to be noted that most of the steps requiring heating were performed under microwave activation, which resulted in quick and efficient reactions.

A related polycyclic *N*-oxide was obtained starting from the *aza*-Baylis−Hillman adduct of 2-nitrobenzaldehyde and ethyl vinyl ketone.[174] A sequence of allylation, RCM, dehydrodesulfinylation/aromatization, and alkylation followed by hydrogenation of the nitro group provided the pyrroloquinoline *N*-oxide (Scheme 92).

5.9. Synthesis of Tetrahydroisoquinolines

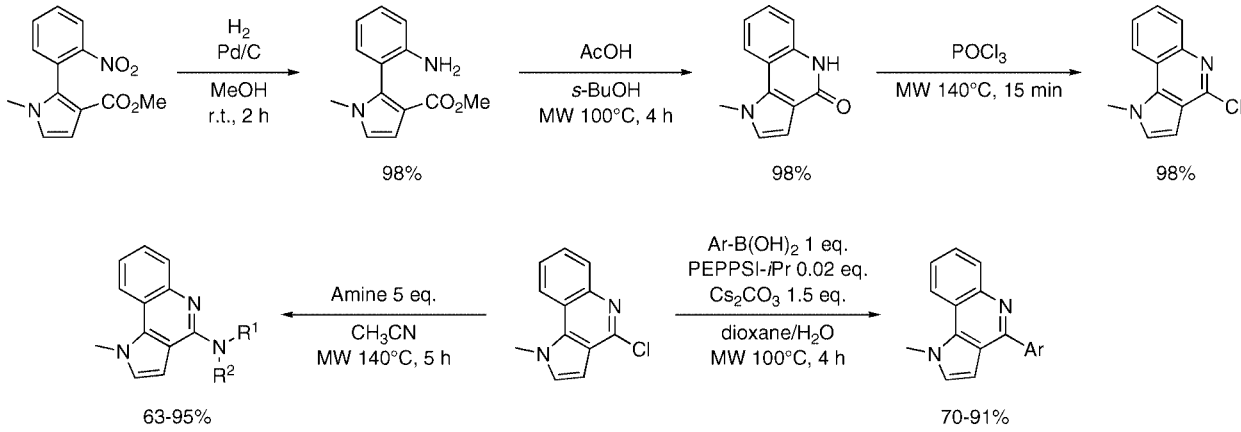
Using palladium-catalyzed chemistry, Kim and co-workers have also investigated the synthesis of isoquinolines.[165] Thus, a Heck reaction of a suitably substituted *N*-allyl β-amino ester led to the formation of a tetrahydroisoquinoline in modest yield (Scheme 93).

Tetrahydroisoquinolines were prepared more efficiently by radical cyclization of type B β-amino esters[175] (Scheme 94) than by intramolecular Heck reaction.

5.10. Synthesis of Indoles and Hydroindoles

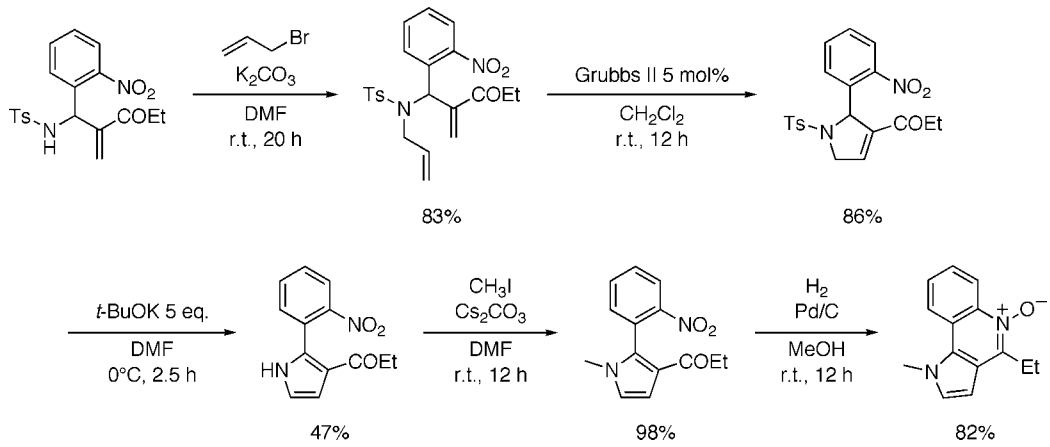
Under palladium-catalyzed conditions, type B β-amino esters produced a mixture of hydroindole and indole via a reductive Heck-type reaction (Scheme 95).[176]

Scheme 91

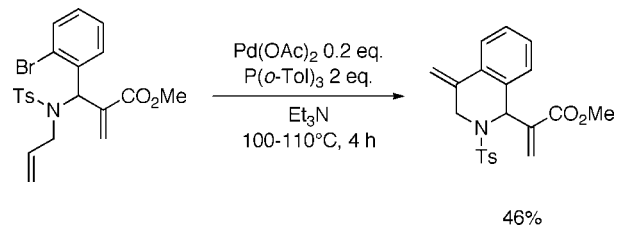


Amine = pyrrolidine, piperidine, 4-methylpiperazine, morpholine, benzylamine, pyrrole
Ar = Ph, *o*-Tolyl, *m*-Tolyl, *p*-Tolyl-, 4-Ph-C_6H_4-, 4-MeO-C_6H_4-, 4-F_3CO-C_6H_4-, 4-F-C_6H_4-, Benzofuran-2-yl, α-Np, 1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalen-6-yl

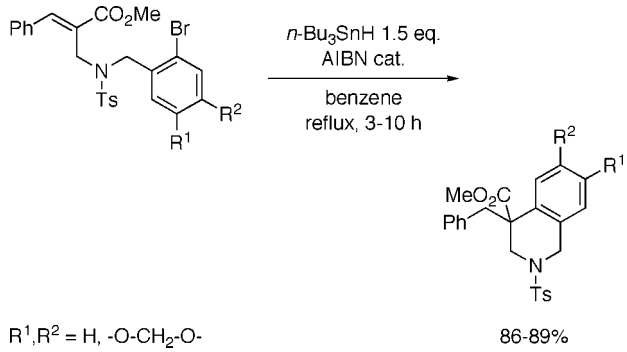
Scheme 92



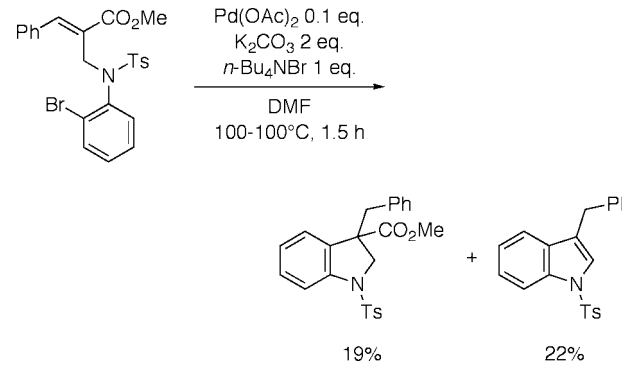
Scheme 93



Scheme 94



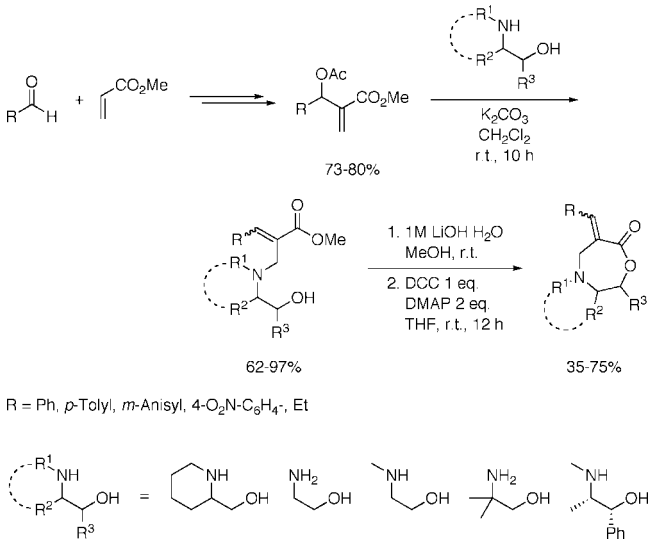
Scheme 95



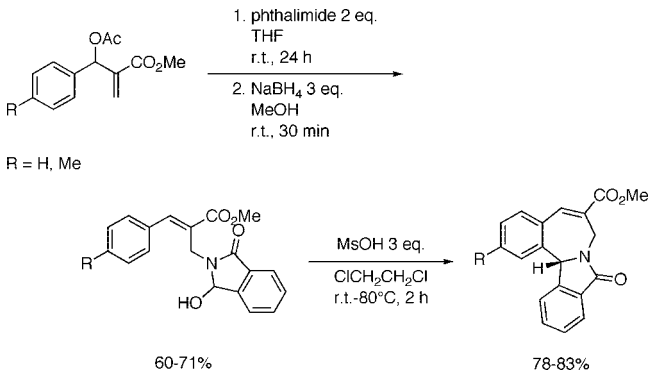
5.11. Synthesis of Oxazepines

Reiser and co-workers have described the synthesis of 1,4-oxazepine-7-ones from type B β-amino esters obtained by displacement of Baylis−Hillman acetates by amino alcohols.[177,178] The method was first developed as a mixture library for the purpose of PEG-supported combinatorial chemistry[177] and then adapted to the solution-phase chemistry.[178] Nucleophilic substitution of Baylis−Hillman acetates by amino alcohols afforded α-alkylidene-β-amino esters in good yields as a mixture of *E* and *Z* stereoisomers. The Baylis−Hillman products derived from aromatic derivatives gave mainly the *E* isomer, whereas aliphatic derivatives gave an equimolar mixture of *E* and *Z* isomers. Saponification of the ester function followed by intramolecular cyclization using DCC gave the 1,4-oxazepin-7-ones (Scheme 96).

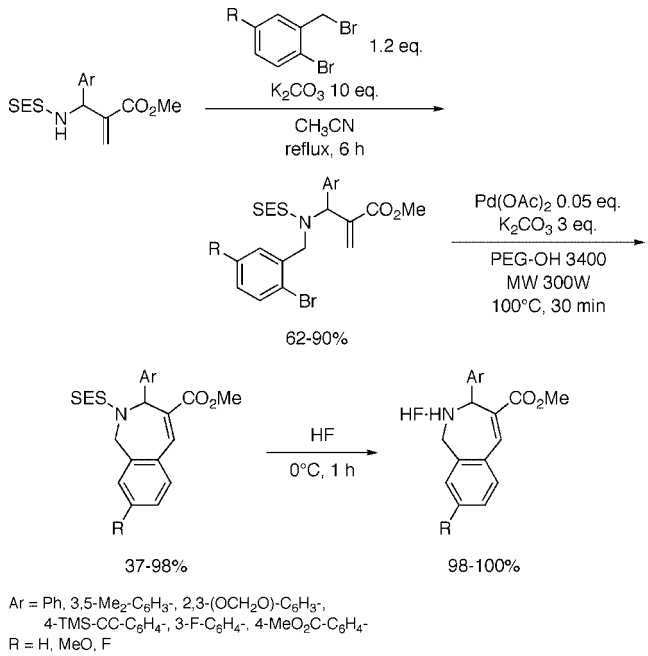
Scheme 96



Scheme 97



Scheme 98



5.12. Synthesis of Benzazepines

Kim and co-workers have described the synthesis of benzazepines from type B β-amino esters protected by a phthalimide group.[179] The strategy implied the reduction of the phthalimide group followed by an intramolecular cyclization in acidic medium via the formation of an iminium ion (Scheme 97).

The group of Lamaty has recently described the synthesis of original benzazepines from SES-protected β-amino esters by an intramolecular Heck reaction.[180,181] Initial study performed on a PEG-supported substrate showed that the PEG played a crucial role on the outcome of the reaction by the formation of palladium nanoparticles.[180] Alkylation of the SES−β-amino esters with a 2-bromobenzyl bromide derivative, followed by an intramolecular Heck reaction using PEG as solvent under microwave irradiation, afforded the benzazepines in good yields (Scheme 98). Deprotection of the SES group was performed quantitatively using neat HF.

5.13. Synthesis of Benzodiazepines

The group of Kim has described the synthesis of benzodiazepines by reaction of Baylis−Hillman acetates and 1,2-phenylenediamine.[182] Saponification of the ester function followed by cyclization using DCC gave the benzodiazepine in good yield (Scheme 99).

Pathak and co-workers have described the synthesis of similar benzodiazepines from substituted 1,2-phenylenediamine derived β-aminocarbonyl compounds.[183] In the case of type A and B β-amino esters, a base-mediated cyclization led to the formation of benzodiazepin-2-ones in good yields, whereas type A β-amino nitriles gave benzodiazepin-2-ylamines upon treatment in acidic medium (Scheme 100). It has to be noted that, under these acidic conditions, type A β-amino nitriles rearranged into type B β-amino nitriles before the cyclization.

5.14. Synthesis of Triazoles

Independently, the group of Sreedhar and the group of Chandrasekhar have developed a multicomponent reaction catalyzed by copper(I) to form 1,2,3-triazoles starting from Baylis−Hillman acetates, sodium azide, and a terminal alkyne (Table 21).[184,185] The reaction implied the in situ formation of an alkyl azide by nucleophilic allylic substitution before the cycloaddition reaction.

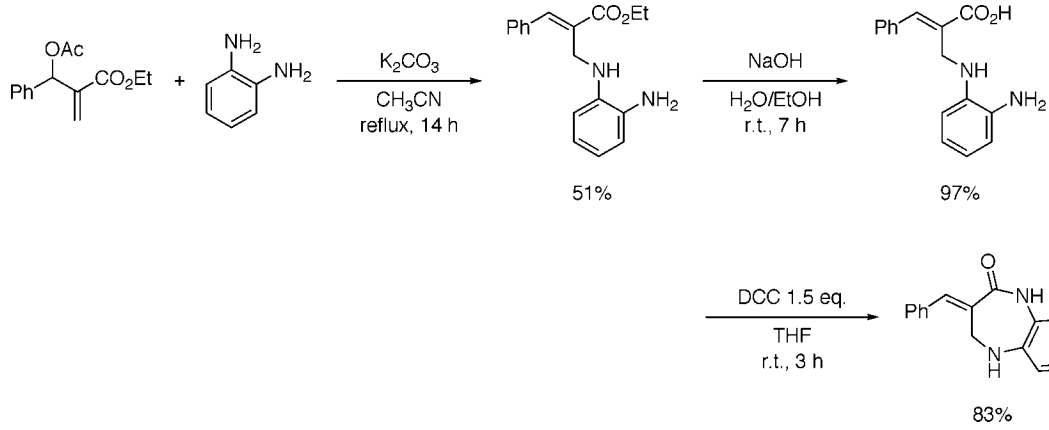
The group of Lee have prepared 1,2,3-triazolobenzazepines by intramolecular cycloaddition of a Baylis−Hillman adducts derived from 2-alkynylbenzaldehydes.[186] The alcohol was first activated as an acetate, and a nucleophilic allylic substitution gave the azide. Intramolecular cycloaddition gave the 1,2,3-triazolobenzazepines in good yields (Scheme 101).

5.15. Synthesis of Uracil Derivatives

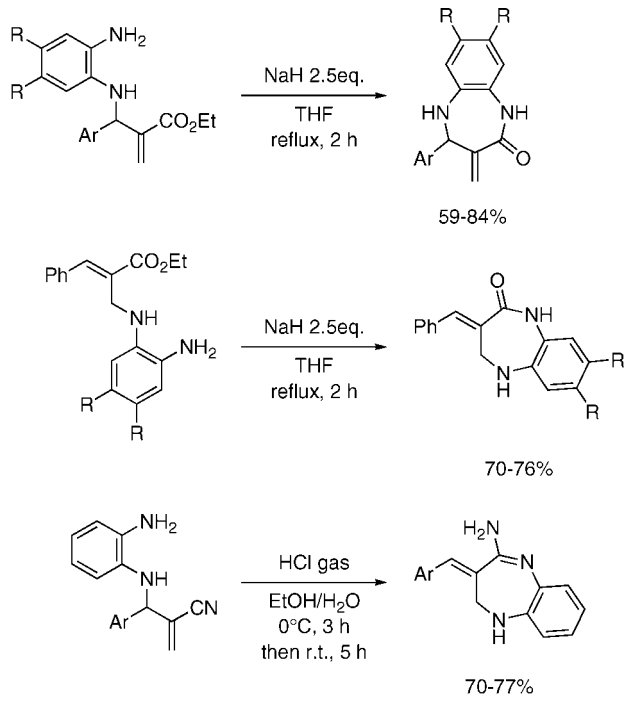
The group of Kim has carried out the synthesis of uracil derivatives starting from type A and B β-amino esters.[187] In both cases, the strategy implied the formation of an urea from the amine function followed by the cyclization of this urea in basic medium (Scheme 102). By using the two sorts of β-amino esters, the strategy allowed the access to a larger variety of products.

Similar compounds have also been prepared from β-amino-β'-hydroxy esters.[188] Treatment of the latter compounds with cyanogen bromide followed by nucleophilic attack of the hydroxyl group, ring-opening, and cyclization allowed the formation of uracil derivatives in good yields (Scheme 103). Alternatively, reaction of β-amino-β'-hydroxy esters with cyanogen bromide under prolonged reaction time yielded

Scheme 99

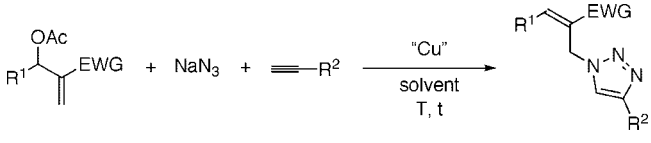


Scheme 100



Ar = Ph, *p*-Tolyl, 2-F-C_6H_4-, 2-Cl-C_6H_4-, 4-Cl-C_6H_4-, 4-Br-C_6H_4-, 2,4-Cl_2-C_6H_3-, 2-Thienyl
R = H, Me, Cl

Table 21. Synthesis of Triazoles from Baylis−Hillman Acetates

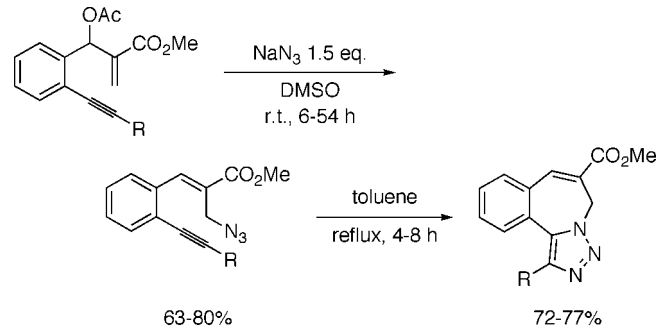


EWG = CO_2Me, CN

"Cu"	reductant	solvent	*T* (°C)	*t* (h)	yield (%)
CuI	Et_3N	H_2O	r.t.	8−12	28−80
CuI		PEG-OH 400	r.t.	6−8	42−93
Cu(0), $CuSO_4$		EtOH	reflux	2−3	70−92

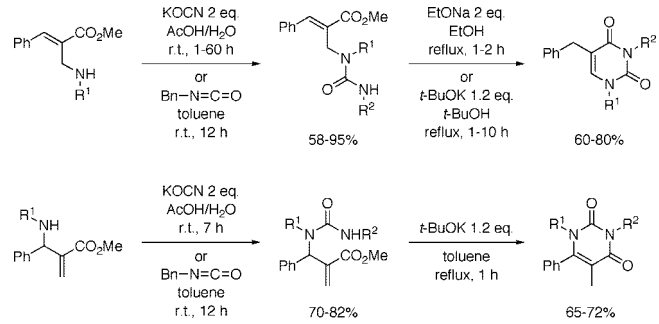
type B β-amino esters urea that cyclized in the presence of NaH (Scheme 103). In contrast, β-amino-β'-methoxy esters and type B β-amino esters gave oximes by cyclization of their *N*-cyano derivatives using hydroxylamine hydrochloride (Scheme 104).

Scheme 101



R = H, Ph, *n*-Bu, CH_2OAc

Scheme 102



R^1 = Ph, Bn, 1-Indanyl
R^2 = H, Bn

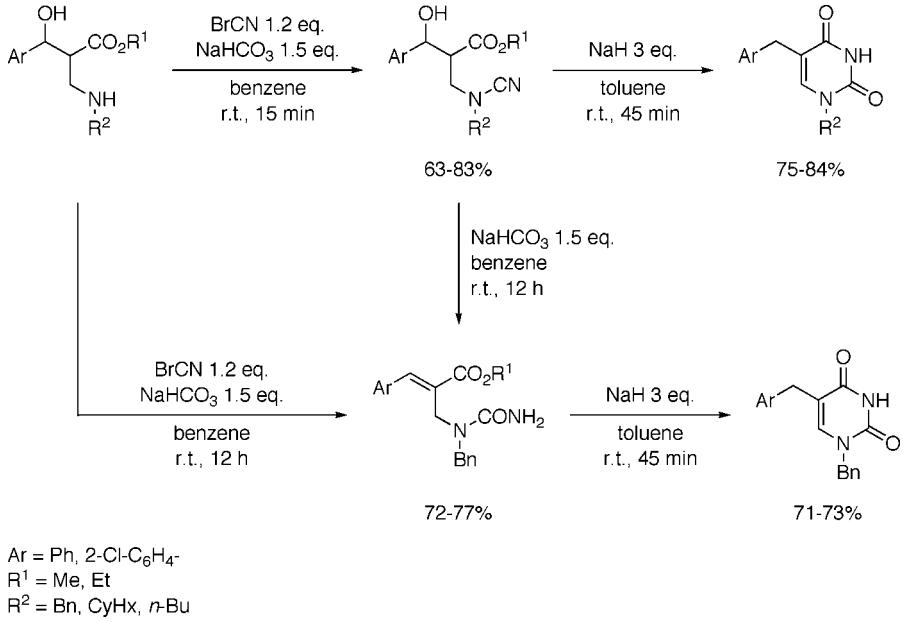
5.16. Synthesis of Pyrimidines and Pyrimidinones

The group of Batra has described the synthesis of ureides from type B β-amino nitriles.[189] The amine function reacted with an isocyanate or an isothiocyanate to give the corresponding urea or thiourea in good yields, which cyclized in basic medium to give 4-iminotetrahydropyrimidin-2-ones in moderate-to-good yields (Scheme 105).

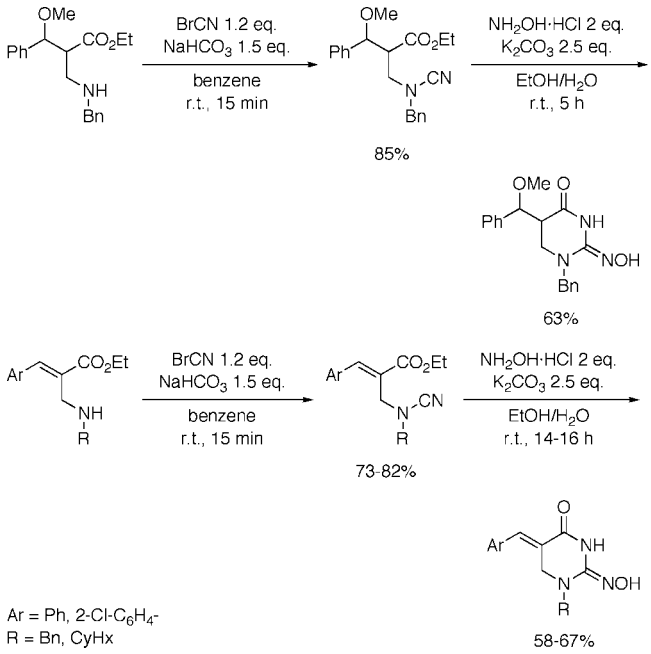
The same group has also described the synthesis of annulated pyrimidones from supported type B β-amino esters.[190] The strategy implied a cyclative cleavage step to give the pyrimidones in good yields (Scheme 106).

Batra and co-workers have studied the synthesis of pyrimidinones and pyrimidines from type B β-aminocarbonyl compounds via *N*-formylation of the amine in the presence of neat formamide followed by ammonium formate-mediated cyclization (Scheme 107).[191] In the case of β-amino nitriles, the *N*-formylation step proceeded efficiently while the cyclization with ammonium formate failed

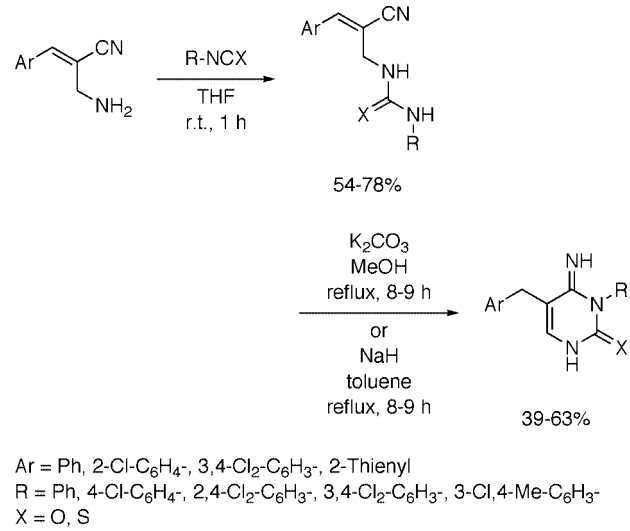
Scheme 103



Scheme 104



Scheme 105



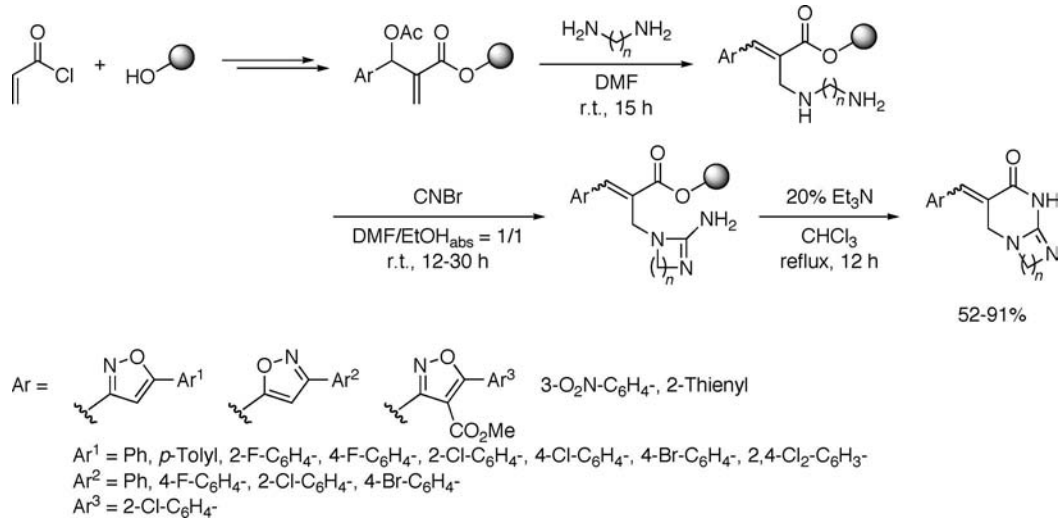
completely to give the 4-aminopyrimidine. When β-amino esters were used, *N*-formylation and cyclization were performed advantageously in a "one-pot" sequential fashion to give the 4-pyrimidones. Chlorination of the latter compounds followed by S_NAr displacement of the chlorine atom with benzylamine provided a new access to 4-aminopyrimidines. Reduction of the nitro substituent in the 2 position triggered an intramolecular cyclization to furnish a pyrimidoquinoline.

Various 2,4,5-trisubstituted pyrimidines were prepared by condensation of amidines or guanidines with type A Baylis−Hillman acetates in refluxing *t*-BuOH (Scheme 108).[192] While condensation of amidines with ester derivatives gave 4-hydroxypyrimidines in good yields except for nonaromatic Baylis−Hillman adducts, *N*,*N*′-diphenylguanidine yielded pyrimidin-4(1*H*)-ones. Condensation of ketone derivatives with amidines produced pyrimidines in modests yields and cyano derivatives gave poor yields for the corresponding 4-aminopyrimidines.

5.17. Synthesis of Fused Pyrimidin-2-ones

Batra and co-workers have described an original approach to various imidazo-[1,2-*a*]-pyrimidinones by cyclization of diaminoesters derived from type A and type B Baylis−Hillman adducts of acrylonitrile (Scheme 109).[193] Conjugate addition of glycine methyl ester on Baylis−Hillman alcohol followed by reduction of the nitrile group and reaction with cyanogen bromide provided the expected imidazo-[1,2-*a*]-pyrimidinones. Alkylation of type B nitriles with ethyl bromoacetate produced an intermediate that was submitted to the same reduction/cyclization sequence. S_N2 displacement of type A acetates with glycine methyl ester, followed by the reduction/cyclization process, produced also imidazo-[1,2-*a*]-pyrimidinones. Using a similar reduction/cyclization sequence, the compound obtained by S_N2 displacement of type A acetates with type B nitrile produced pyrimido-[1,2-*a*]-pyrimidin-2-ones (Scheme 110).[193]

Scheme 106



This group has also described the synthesis of imidazo[1,2-*a*]pyrimidin-7-ylamines starting from type B β-amino nitriles substituted by a dimethoxyethyl group (Scheme 111).[194] Reaction of these compounds with cyanamide followed by acidic treatment produced 2-aminoimidazoles that, upon treatment with sodium methanolate, gave imidazo[1,2-*a*]pyrimidin-7-ylamines. With β-amino nitriles substituted by a heteroaromatic group, imidazo[1,2-*a*]pyrimidin-7-ylamines were obtained directly after the acidic treatment.

5.18. Synthesis of Pyrrolizinones

Batra and co-workers described the synthesis of pyrrolizinones starting from type B β-amino esters (Scheme 112).[191] Treatment of β-amino esters with tetrahydro-2,5-dimethoxyfuran produced pyrrolo derivatives. Saponification of the latter compounds followed by PPA-mediated cyclization gave the original pyrrolizinones.

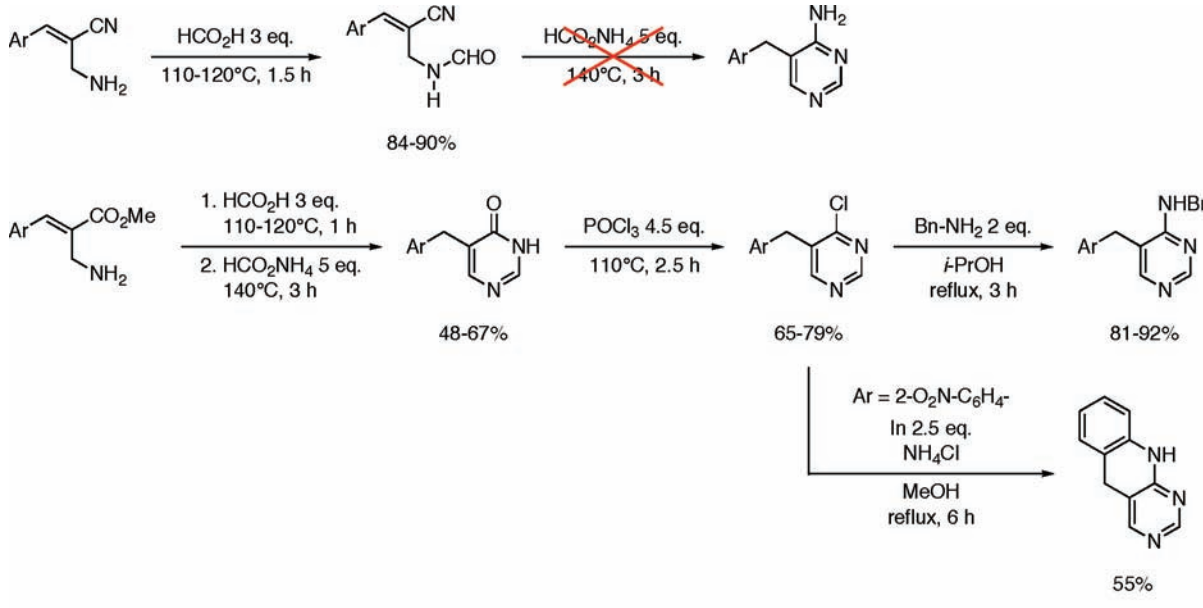
5.19. Miscellaneous Heterocycles

The group of Vasudevan has described the synthesis of heterocyclic scaffolds from β-amino esters by an intramolecular Heck reaction under microwave irradiation.[195] β-amino esters bearing a halogen atom on the 2 position of the sulfonamide moiety led to the formation of 7-membered ring sultams, whereas β-amino esters bearing a halogen atom on the 2 position of the aryl substituent led to the formation of indenes in moderate-to-good yields (Scheme 113).

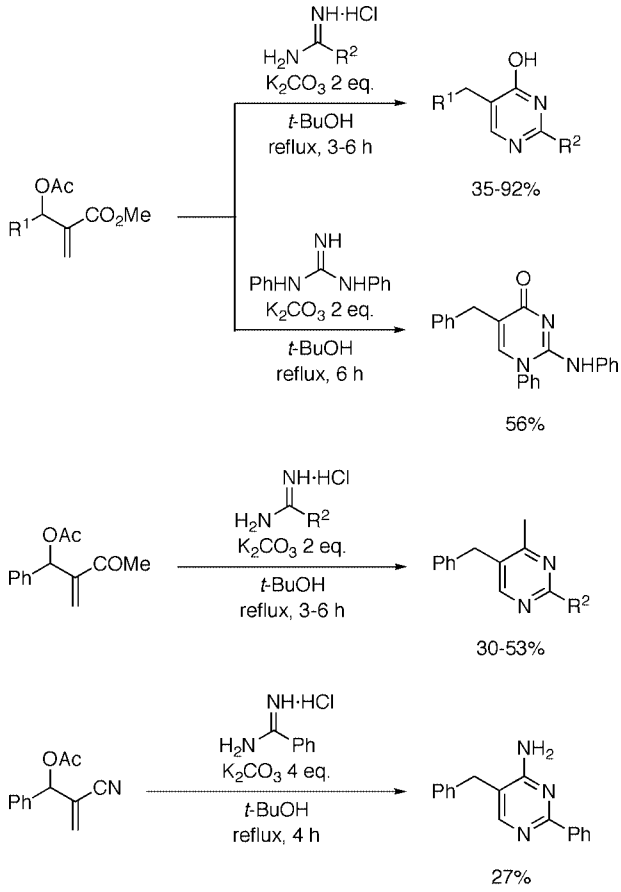
Kim and co-workers have reported the formation of 4-oxa-9-azafluorene-3,9-diones from phthalimido-β-amino esters.[179] The strategy implied a reduction of the phthalimido group followed by an intramolecular transesterification in acidic medium (Scheme 114). Similar products can be obtained by treatment of type B phthalimido-β-amino esters with trifluoroacetic acid by direct transesterification (Scheme 114).

Kim and co-workers have studied the reaction of type A β-amino esters in polyphosphoric acid.[169] When the

Scheme 107



Scheme 108



R^1 = Ph, *p*-Tolyl, β-Np, *n*-C_5H_{11}-
R^2 = Ph, Me

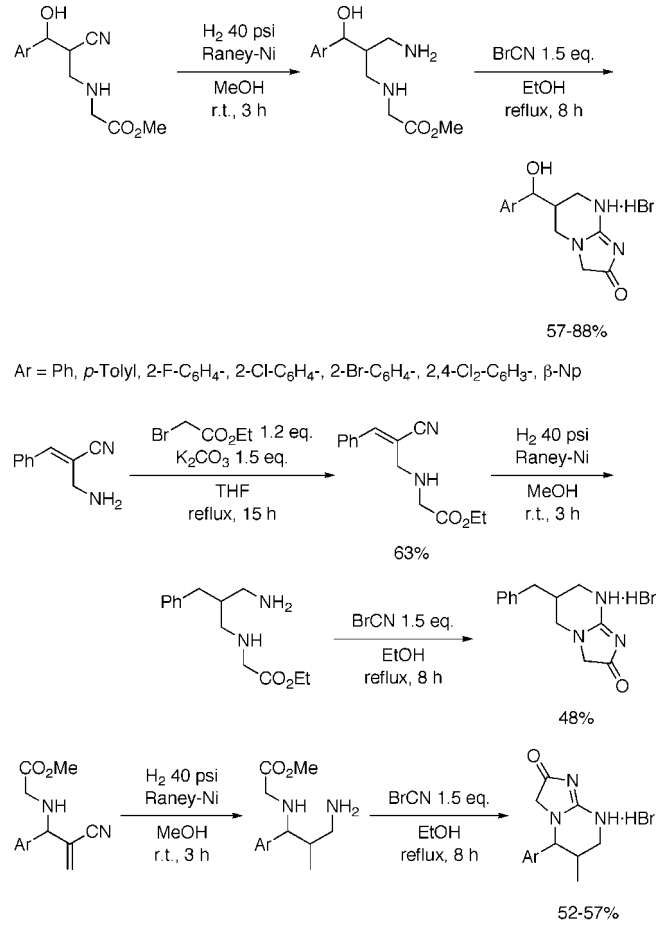
aniline moiety is not substituted or when it bears electron-withdrawing groups, the reaction gave substituted quinolines (see section 5.7). In contrary, when the aniline moiety is substituted by electron-releasing groups, the reaction furnished a mixture of indanone and indenoindenone. The indanone was formed by a Claisen rearrangement followed by an intramolecular Friedel−Crafts acylation, whereas the indenoindenone was formed by a Claisen rearrangement followed by an intramolecular Michael-type addition and an intramolecular Friedel−Crafts acylation (Scheme 115).

This group has also studied the reactivity of similar type B β-amino esters in polyphosphoric acid.[196] At 120 °C, the double bond of type B β-amino esters can be isomerized to generate an iminium ion, which can react by an intramolecular aromatic Mannich-type reaction. A subsequent Friedel−Crafts reaction gave the tetrahydroindeno[1,2*b*]-quinolin-10-ones. In a secondary reaction pathway, type B β-amino esters are subjected to a Friedel−Crafts reaction followed by a 1,3-proton transfer. A second Friedel−Crafts reaction followed by a dehydration gave a 7*H*-indeno[2,1*c*]-quinoline (Scheme 116).

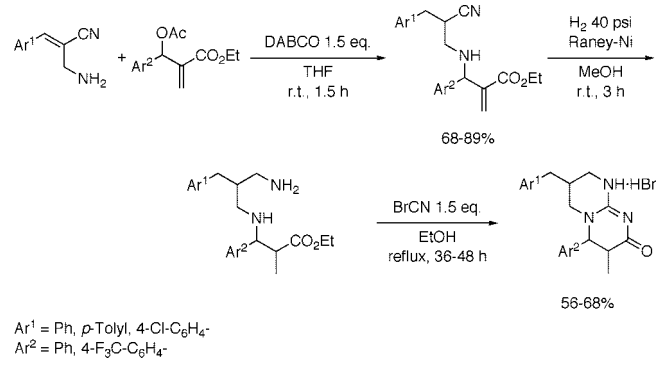
Recently, Kim and co-workers have described the synthesis of dihydropyrido[2,1*a*]isoindolone derivatives by radical cyclization of type B enamide derived from Baylis−Hillman adducts of 2-bromobenzaldehydes (Scheme 117).[197]

Under palladium catalysis, these type B enamides react in a different pathway, leading to the formation of benzoazepino[2,1-*a*]isoindoles (Scheme 118).[198] In this process, two sequential carbopalladations produced the

Scheme 109



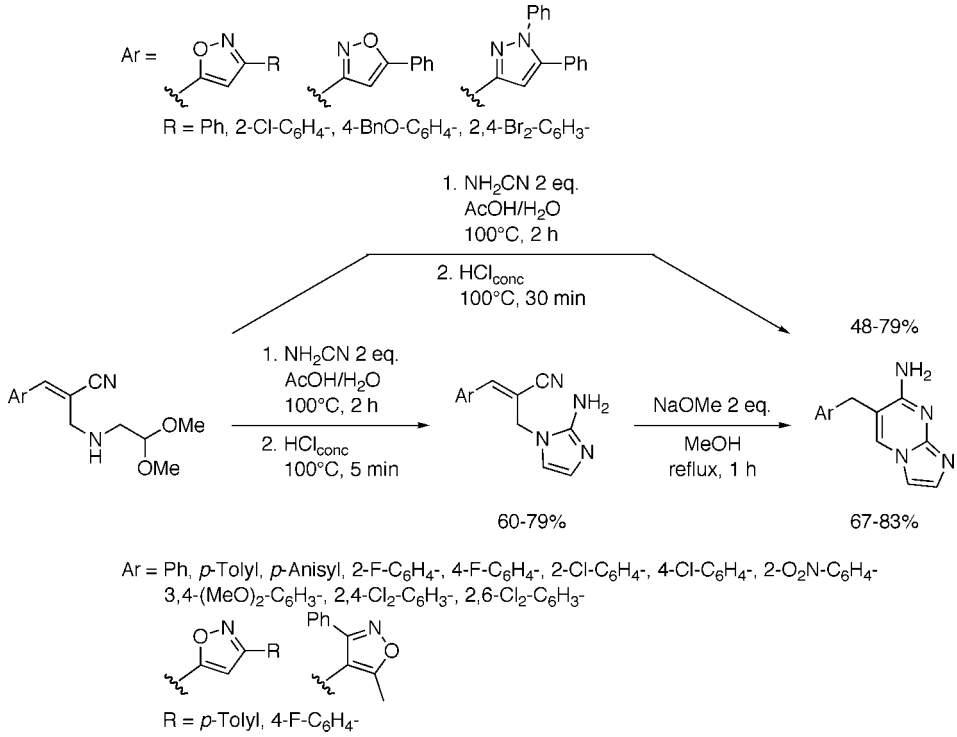
Scheme 110



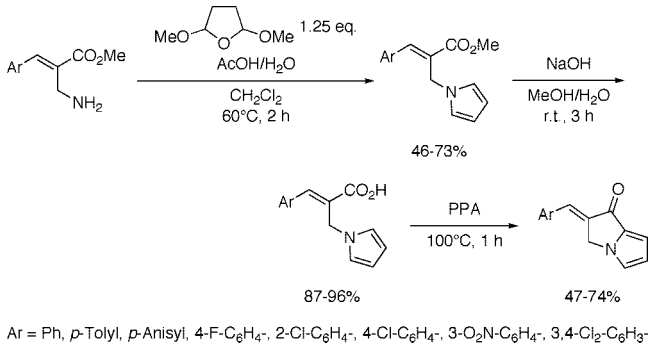
bridged benzoazepino[2,1-*a*]isoindole derivatives. However, when the enaminone moiety possessed an alkyl group, a β-elimination occurred faster than the second carbopalladation, and nonbridged benzoazepino[2,1-*a*]isoindoles were obtained.

Starting from indole derivatives of type B β-amino esters, Kim and co-workers prepared another series of benzoazepino[2,1-*a*]indoles (Scheme 119).[199] For indole derivatives with no substituent on position 2, a palladium-catalyzed intramolecular cyclization occurred in this position to give benzoazepino[2,1-*a*]indoles derivatives. When a methyl group is present in this position, the cyclization occurred on position 6 to produce eight-membered compounds.

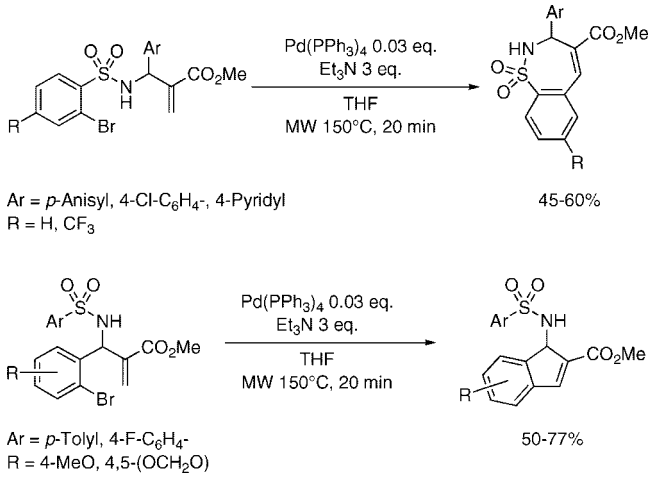
Scheme 111



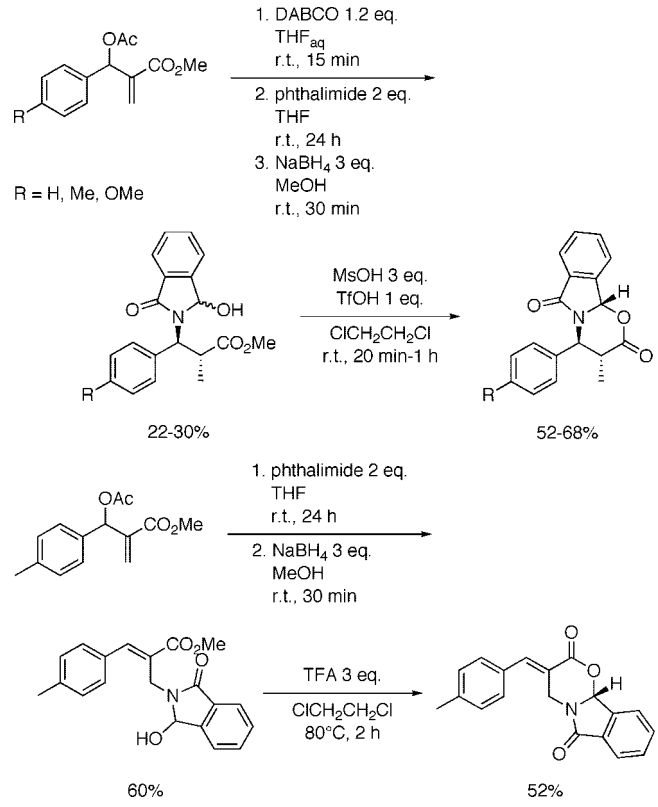
Scheme 112



Scheme 113



Scheme 114

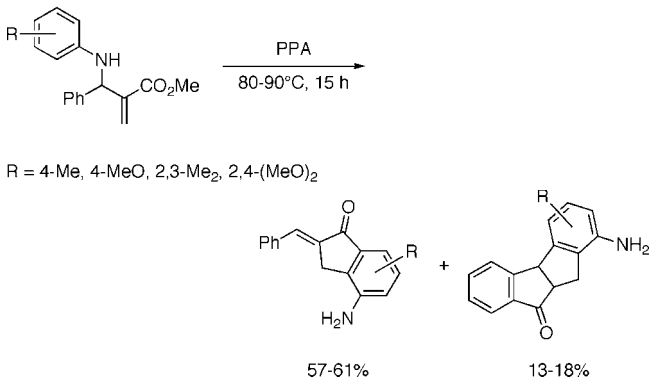


6. Conclusion

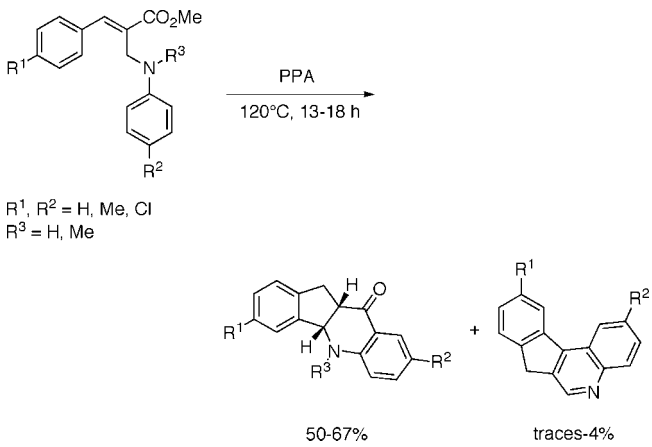
The *aza*-Baylis−Hillman reaction by introducing a nitrogen atom in a molecule is expanding the scope of the Baylis−Hillman reaction. The last five years have seen a rapid growth in the applications of the *aza*-Baylis−Hillman reaction. Great progress has been made to expand the scope of the reaction to various Michael acceptors and to improve the reaction rate. Still, the reaction mechanism needs to be studied further to address reaction rate issues.

Efforts have also been devoted to the development of the asymmetric version of the reaction, especially in the design of proper organocatalysts. If it is now possible to obtain good

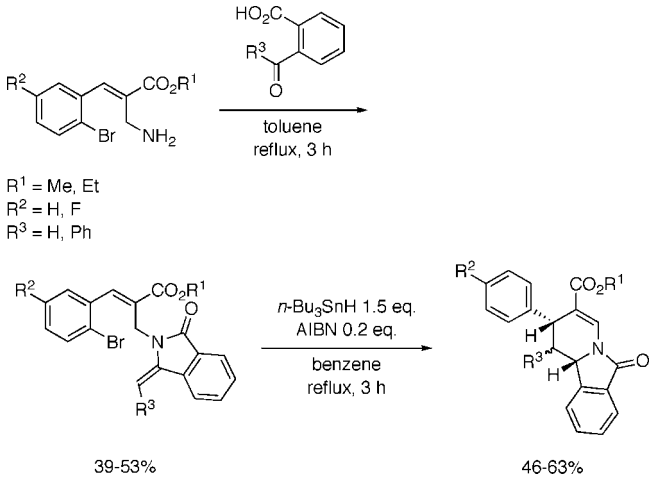
Scheme 115



Scheme 116



Scheme 117

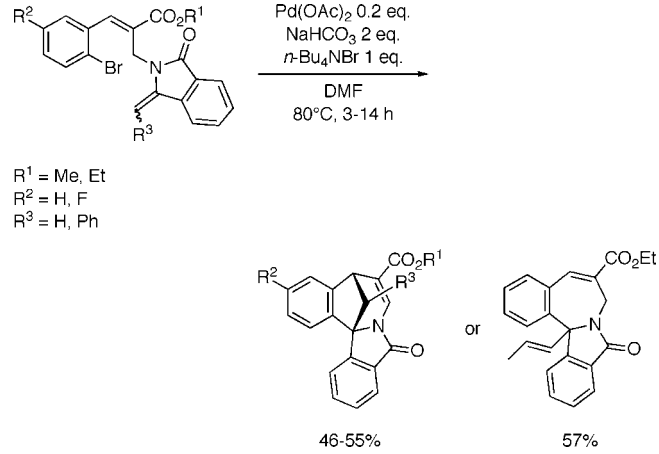


enantioselectivities, yields are generally fair but the reaction is not as efficient with every Michael acceptor.

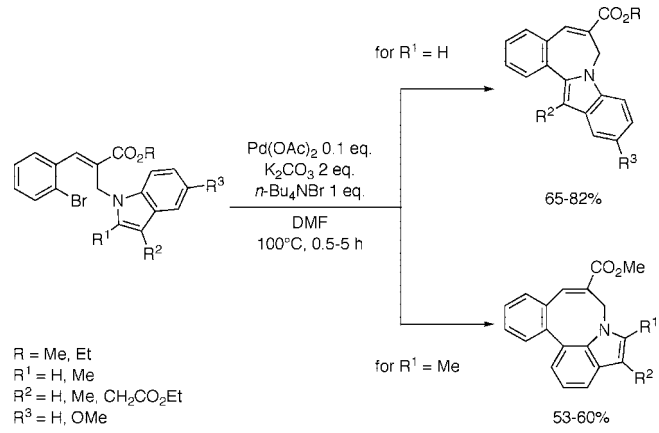
aza-Baylis−Hillman products are multifunctional synthons that have been used to synthesize various compounds, especially peptidomimetics and a wide variety of heterocyclic structures.

Although many studies have been carried on the *aza*-Baylis−Hillman reaction, this reaction continues to attract organic chemists' attention and is still a very active research topic. This reaction has not been fully exploited, and these *aza*-Baylis−Hillman adducts could serve as templates to synthesize various heterocyclic compounds. This efficient and atom-economic reaction combined with other transformations gives a facile access to very complex molecules and finds wide applications in organic synthesis.

Scheme 118



Scheme 119



7. Abbreviations

AcO	acetate
acac	acetylacetonate
AIBN	azobisisobutyronitrile
BEMP	2-(*tert*-butylimino)-2-(diethylamino)-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
Boc	*tert*-butyloxycarbonyl
Boc_2O	di-*tert*-butyldicarbonate
BOPCl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
Bs	benzenesulfonyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
Bt	benzotriazole
Bz	benzoyl
CAN	ceric ammonium nitrate ($(NH_4)_2Ce(NO_3)_6$)
CDI	carbonyldiimidazole
cod	*cis*,*cis*-1,5-cyclooctadiene
m-CPBA	*m*-chloroperbenzoic acid
CPME	cyclopentenylmethylether
CyHx	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DAST	*N*,*N*′-diethylaminosulfide trifluoride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DEAD	diethyl azodicarboxylate
DHP	dihydropyrane
DIAPHOX	diaminophosphine oxides
DIBAL-H	diisobutylaluminium hydride
DIC	*N*,*N*′-diisopropylcarbodiimide
DIEA	diisopropylethylamine

DIFLUORPHOS	[(4,4′-bi-2,2-difluoro-1,3-benzodioxole)-5,5′diyl]bis(diphenylphosphine)
DIPAMP	ethylenebis[(2-methoxyphenyl)phenylphosphine]
DMAP	4-(dimethylamino)pyridine
DMF−DMA	*N*,*N*-dimethylformamide dimethylacetal
dppb	1,4-bis(diphenylphosphino)butane
ee	enantiomeric excess
EWG	electron-withdrawing group
HMPA	hexamethylphosphoramide
HOAt	1-hydroxy-7-azabenzotriazole
HOBt	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
3-HQD	3-hydroxyquinuclidine
β-ICD	β-isocupreidine
JJ	*J*anda*J*el
LBBA	Lewis base−Brønsted acid
LDA	lithium diisopropylamide
LG	leaving group
Ms	mesyl
MS	molecular sieves
MtOA	methyltrioctylammonium
MW	microwave
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
α-Np	α-naphthyl
β-Np	β-naphthyl
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine *N*-oxide
Ns	nosyl (4-nitrobenzenesulfonyl)
Nu	nucleophile
PEG	polyethylene glycol
PEPPSI-*i*Pr	[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride
Phth	phthaloyl
PMP	*p*-methoxyphenyl
PPA	polyphosphoric acid
PTA	1,3,5-triaza-7-phosphaadamantane
PyBroP	bromotris(pyrrolidino)phosphonium hexafluorophosphate
QD	quinuclidine
SES	2-[(trimethylsilyl)ethane]sulfonyl
TFA	trifluoroacetic acid
THP	tetrahydropyranyl
TfO	triflate
TMS	trimethylsilyl
Triton B	benzyltrimethylammonium hydroxide
Ts	tosyl
Z	benzyloxycarbonyl

8. Note Added in Proof

Since the submission of the accepted version of the manuscript, several relevant publications have appeared on various aspects of this fascinating reaction. The use of nanocrystalline magnesium oxide (NAP-MgO) as an alternative catalyst provided good results in the *aza*-Baylis–Hillman reaction of cyclic enones with tosylimines.[200] *N*-Carbamate α-amidoalkyl sulfones were used as precursors of carbamate-protected imines in the *aza*-Baylis–Hillman reaction.[201,202] When chiral *N*-thiophosphorylimines were used in the reaction with methyl vinyl ketone catalyzed by PTA, adducts were obtained in moderate-to-good de.[203] High ee's were obtained in the *aza*-Baylis–Hillman reaction of PMP–sulfonylimines with β-naphthyl acrylate catalyzed by bifunctional β-isocupreidine derivatives.[204] The use of chiral NHCs prepared form L-pyroglutamic acid as catalyst in the reaction of cyclopentenone with tosylimines gave low enantiomeric excesses.[205] *Aza*-Baylis–Hillman adducts of cyclic enones were alternatively prepared by $FeCl_3$-mediated amination of the corresponding hydroxy derivatives.[206] An asymmetric [1,3]-sigmatropic rearrangement of *O*-trichloroacetimidate derivatives of Baylis–Hillman adducts catalyzed by dimeric cinchona alkaloids yielded the *aza*-derivatives in high ee.[207] Ts-protected α-methylene-β-aminoesters were used as substrates in a Heck reaction to prepare β-aryl substituted *N*-tosyl *aza*-Baylis–Hillman adducts.[208] Type B *aza*-Baylis–Hillman derivatives were used for the synthesis of various pyrimido[2,1-*b*]quinazoline derivatives.[209] Isatin, benzimidazole, and imidazole derivatives of type B β-aminoesters furnished various seven- and eight-membered cyclic compounds.[210]

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