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Recent advances in tertiary amine Lewis base-promoted cycloadditions of allenoates

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ABSTRACT

Lewis base-catalyzed annulations of allenoates have been one of the most powerful synthetic strategies for the synthesis of various valuable cycles, especially in the preparation of biologically active natural products and pharmaceuticals. Generally, the effective Lewis bases mainly include tertiary phosphine, NHC and tertiary amine catalysts, among those catalysis, tertiary amine Lewis bases have proven to be effective catalysts for a range of synthetic transformations. In the past decades, tremendous progress involving tertiary amines-promoted cycloaddition of allenoates has been made in the chemoselective construction of valuable motifs. This review describes a comprehensive and updated summary of tertiary amine Lewis base-promoted annulation reactions of allenoates. Diverse reactivities, chemoselectivties and detailed reaction mechanisms will be highlighted in this review.

1. Introduction

Cycloadditions are among the most reliable bond-forming strategies in organic synthesis, and are widely used in synthesizing various valuable cycles in a single step, especially in the preparation of pharmaceuticals, bioactive natural products and agrochemicals [1,2]. In the past several decades, synthetic chemists have made tremendous efforts to explore novel synthetic strategies and resolve the challenging problems in classic cycloadditions by using different catalytic systems involving metal catalysis, enzyme catalysis and organocatalysis. Among these fields, organocatalytic cycloaddition reaction, with its advantages of being environmentally friendly, having metal free residues, requiring simple and mild reaction conditions, has recently emerged as one of the most powerful catalytic strategies for the construction of carbo- and hetero-cycles. Lewis base catalysis, as a class of organocatalysis, occupies a preeminent position since the Rauhut–Currier reaction [3] and Morita–Baylis–Hillman reaction [4] are discovered in the 1960s. In particular, Lu and coworkers were the first to report the phosphine-catalyzed [3 + 2] cycloaddition reaction of activated alkenes in 1995 [5], and Lewis base catalysis has attracted interest from a large number of research groups. Many Lewis bases promoted cycloadditions of electro-deficient alkenes, allenoates, alkynes and MBH derivatives have been discovered in laboratories worldwide [6–16].

The conformations of tertiary amines are pyramidal and have a pair of nonbonding electron pairs, which represent the most commonly recognized form of Lewis base catalysts. With the development of Lewis base-catalyzed cycloaddition, tertiary amine catalysts have proven to be effective catalysts for a range of synthetic transformations. Usually, tertiary amines are generally more basic and less nucleophilic than similarly organophosphines, which show different catalytic reactivities and selectivities in the reactions. Thus a review focusing on amines as Lewis base catalysts in the reactions of electron-deficient olefins is highly desirable [17].

Allenoates, as a class of electron-deficient olefins, are attractive substrates for Lewis base catalysis due to their diverse reactivities. As illustrated in Scheme 1, nucleophilic addition of a tertiary amine catalyst to the electrophilic β-carbon of allenoate results in the generation of a zwitterionic intermediate. The zwitterionic intermediate can be depicted in several ways, including anion localization at the α-carbon, γ-carbon or delocalized, as C1, C2 or C3 synthons (Scheme 1). Considering these resonance structures, it is easy to understand the versatile reactivities of allenoates in the presence of different electrophilic–coupling partners.

In this review, we summarize recent progresses in tertiary amine Lewis base-promoted cycloadditions of allenoates. The diverse reactivity, various reaction modes and proposed mechanisms will be described in detail in the review. We hope that this tutorial review provides our readers with a systematic picture of this

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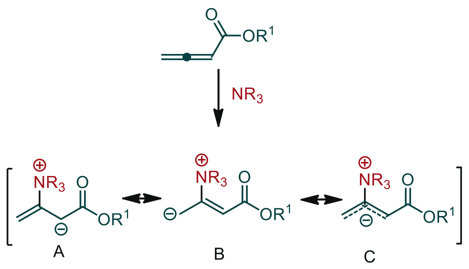
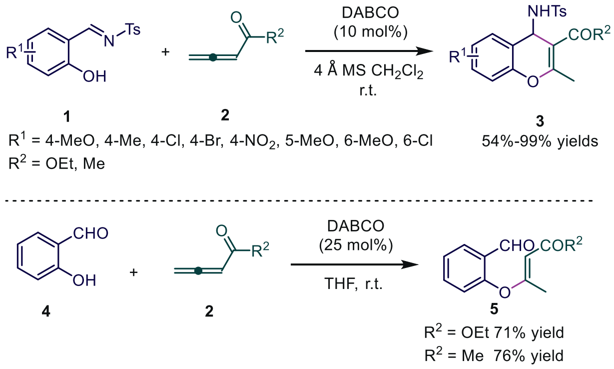


Scheme 1. Reactivity of allenoates in the presence of a tertiary amine.



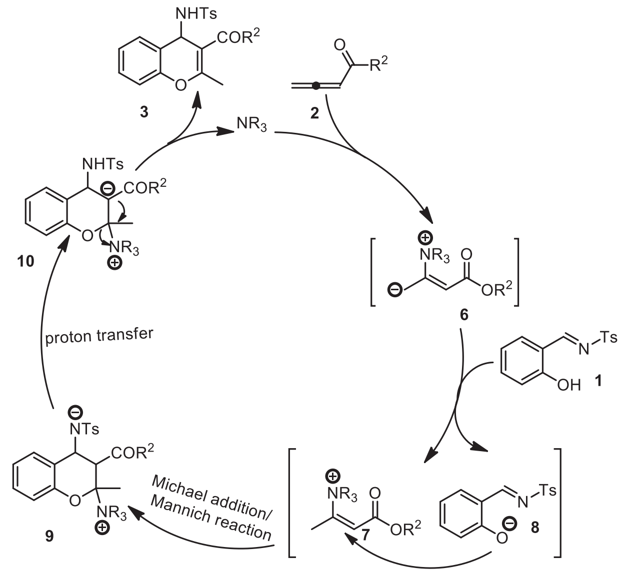
Scheme 2. DABCO-catalyzed [4 + 2] cycloaddition of allenoates/penta-3,4-dien-2-one with salicyl *N*-tosylimine.

research field, leading to further development in the reporting of these new reaction modes.

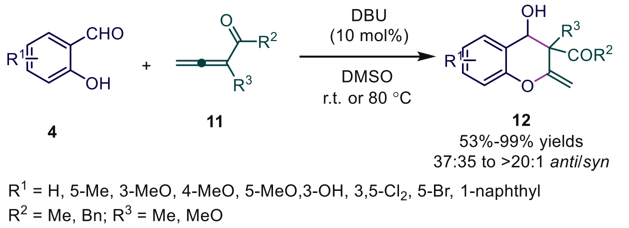
2. Tertiary amine-catalyzed [4 + 2] cycloaddition of allenoates with electrophiles

As early as 1988, Tsuboi and coworkers first reported a DABCO-catalyzed Morita–Baylis–Hillman reaction of allenoates with aldehydes [18]. DABCO-catalyzed [4 + 2] cycloaddition of allenoates was first discovered in 2005. In the literature, Shi and coworkers used ethyl 2,3-butadienoate/penta-3,4-dien-2-one and salicyl *N*-tosylimines as reactive substrates to give highly functionalized chromene derivatives **3** in good to excellent yields [19]. The authors found that molecular sieves of 4 Å as a desiccant could prevent the decomposition of imines by ambient moisture and improve the yield. Interestingly, allenoates were used as a novel C2 synthon in the [4 + 2] cycloaddition. However, the authors used salicylaldehyde **4** as a substrate instead of salicyl *N*-tosylimines **1**, and the corresponding Michael addition product **5** was formed rather than chromenes. The authors thought that the alkoxide adduct formed by the aldol reaction underwent proton transfer more slowly than the sulfonamide anion counterpart; and retro-aldol reaction effectively competed to give the starting anion, and direct elimination of DABCO occurred to provide the product **5** (Scheme 2).

The authors proposed a plausible reaction mechanism. As illustrated in Scheme 3, nucleophilic attack of the tertiary amine with the allenoate generated a zwitterionic intermediate **6**, which deprotonated the phenol group in imine **1** to give intermediates **7** and **8**. Next, a tandem Michael addition/ Mannich reaction, followed by proton transfer and elimination, produced chromene **3** and regenerated the catalyst. Accounting for the longer reaction time required for imines with electron-withdrawing groups on the benzene rings because of the decreased nucleophilicity of the oxygen atom, the authors thought that the Michael addition step might be the rate-determining step (Scheme 3).



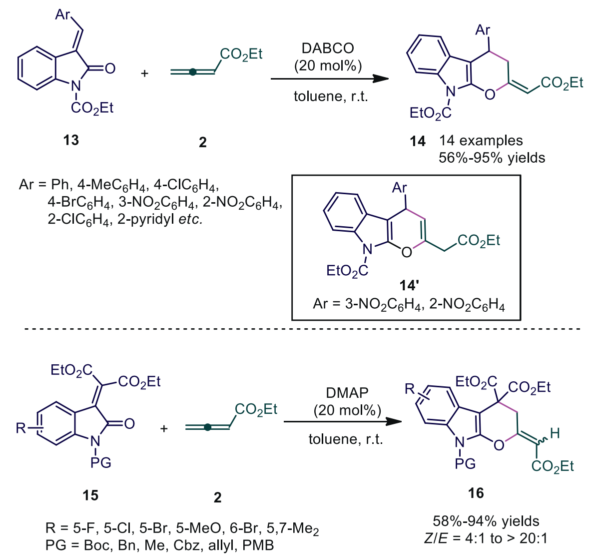
Scheme 3. Plausible reaction mechanism for DABCO-catalyzed [4 + 2] cycloaddition of salicyl *N*-tosylimines.



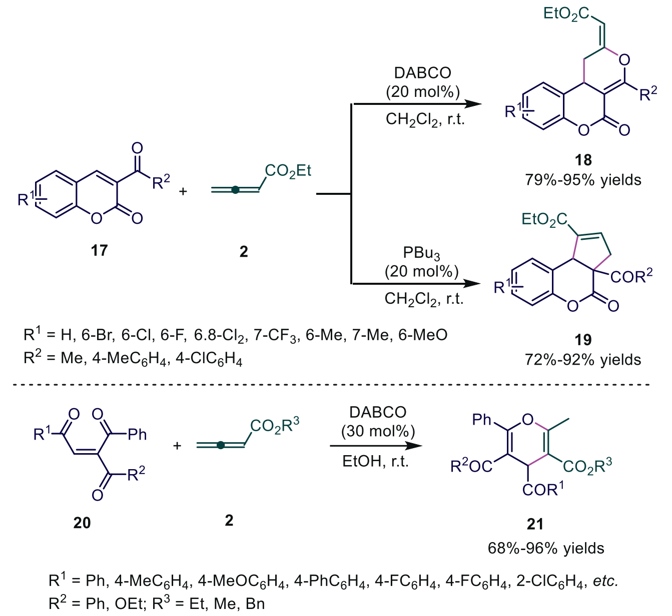
Scheme 4. DBU-catalyzed [4 + 2] cycloadditions of salicylaldehydes.

Based on previous work, Shi and coworkers wished to realize tertiary amine-catalyzed cycloadditions of salicylaldehydes with allenoates [20]. By screening different allenoates, the authors found that 3-methylpenta-3,4-dien-2-one, 3-benzylpenta-3,4-dien-2-one, or ethyl 2-methylbuta-2,3-dienoate **11** with salicylaldehydes **4** were used in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and the [4 + 2] cycloaddition reaction proceeded smoothly, providing the corresponding functionalized 2*H*-1-chromenes **12** in good to excellent yields with moderate to good diastereoselectivities. This experiment suggested that the temperature played a very important role in the diastereoselectivity of this reaction. Only an *anti*-adduct was obtained when the temperature was increased to 80 °C, albeit with a slightly lower yield (81% yield). While the reaction occurred at 20 °C, **12** was obtained in 99% yield as a pair of diastereoisomers (*anti*/*syn*: 74:25) (Scheme 4).

According to Shi's report, α and β sites of allenoates participate in the formation of chemical bonds. Owing to the multiple reactive sites of allenoates, synthetic chemists have wanted to explore novel bonding strategies. In 2011, Ye and Wang reported novel DABCO-catalyzed [4 + 2] cycloadditions of allenoates with arylidenoxindoles, affording the corresponding dihydropyran-fused indoles **14** in good yields with exclusive regio- and diastereoselectivities [21]. In this report, the novel β and γ sites of allenoates participated in the formation of chemical bonds. Further study showed that the electrical properties of substituents on arylidenoxindoles had a significant influence on selectivity, and mixtures (desired adducts **14** and double bond migrated isomers **14′**) were obtained in 67% and 65% yields, respectively, when strong electron-withdrawing groups (3-NO_2, 2-NO_2) were introduced. Almost simultaneously, Shi and coworkers reported the DMAP-catalyzed regioselective [4 + 2] cycloaddition of isatin-derived α,β-unsaturated



Scheme 5. DABCO or DMAP-catalyzed [4 + 2] cycloadditions of allenoates with oxindoles.

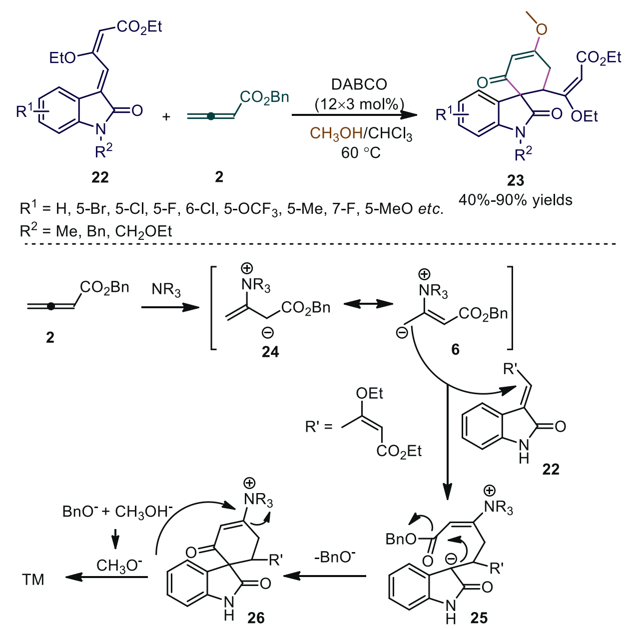


Scheme 6. DABCO or PBu_3 catalyzed [4 + 2] or [3 + 2] cycloadditions of 3-acyl-2*H*-chromen-ones with ethyl 2,3-butadienoate.

diesters with ethyl 2,3-butadienoate, affording the corresponding cyclic products **16** in good to excellent yields under mild conditions (Scheme 5) [22].

In 2012, Shi and coworkers developed highly regioselective [4 + 2] and [3 + 2] cycloadditions of 3-acyl-2*H*-chromen-ones with ethyl 2,3-butadienoate catalyzed by DABCO and Bu_3P, respectively, giving dihydropyran-fused and cyclopenten-fused chromen-2-one derivatives in moderate to excellent yields [23]. Later, the authors applied 3-acyl(or alkoxycarbonyl)-1,4-enediones with 2,3-butadienoates as reactive substrates, finishing an efficient DABCO-catalyzed [4 + 2] cycloaddition of 3-acyl(oralkoxycarbonyl)-1,4-enediones with 2,3-butadienoates. In this report, α and β sites of allenoates participated in the formation of chemical bonds (Scheme 6) [24].

Spirooxindoles are ubiquitous motifs of biologically active compounds [25–28]. Because of their considerable medicinal potential, researchers have made efforts to develop efficient synthetic modes for the construction of spirooxindole scaffolds. In 2016, Meng and coworkers reported novel DABCO-catalyzed [4 + 2] cycloadditions of methyleneoxindoles and allenoate [29,30]. The experiment results showed that 2,3-butadienoate first acted as a novel C4 synthon in a tertiary amine-catalyzed reaction, and the methoxy group acted as a nucleophilic reagent and appeared in the final product. The authors proposed a plausible mechanism for this domino reaction. First, acting as a nucleophilic trigger, DABCO attacked the β carbon of the allenoate to produce intermediates **24** and **6**. Subsequently Michael addition/intramolecular cyclization gave intermediate **26**. Finally, the nucleophilic reagent (CH_3O-) attacked **26** to give the desired product and regenerated DABCO (Scheme 7).

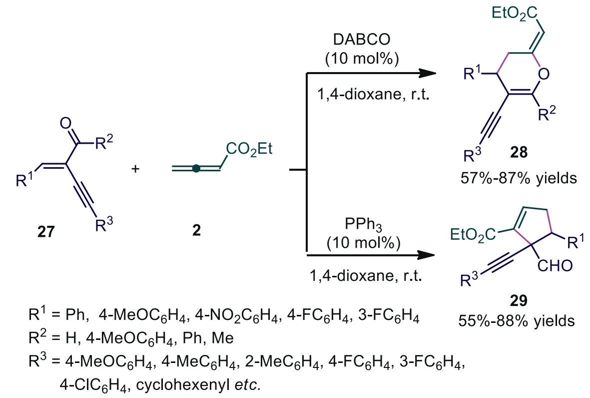


Scheme 7. DABCO-catalyzed [4 + 2] cycloadditions of methyleneoxindoles and allenoate.

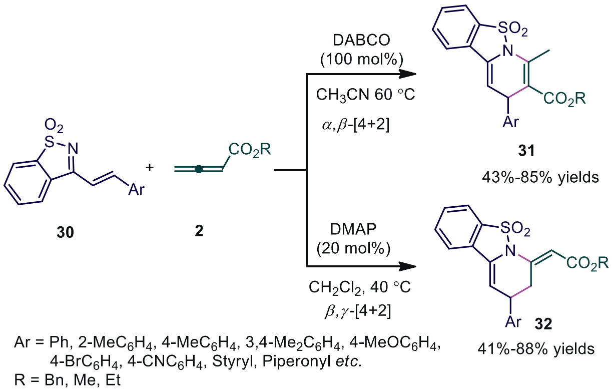
Catalyst-controlled regiodivergent cycloaddition has been a practical method to construct valuable cyclic skeletons in organocatalysis fields. In 2015, Swamy and co-workers reported divergent synthesis of functionalized dihydropyran derivatives and 1,1-alkyne (aldehyde)-substituted cyclopentenes by applying phosphine or amine Lewis base catalysts [31]. When DABCO was used as the catalyst, [4 + 2] cycloaddition occurred, providing dihydropyran derivatives in 57%-86% yields. Meanwhile, [3 + 2] cycloaddition adducts were obtained in the presence of phosphines. It was noted that only enynals were used as reactive substrates, and phosphine-catalyzed [3 + 2] cycloaddition could proceed smoothly. The authors also attempted the reaction of allenoate **2a** and enynal **27a** by using simple chiral amines (20 mol%) in 1,4-dioxane as the solvent, and cycloaddition adduct **28a** was obtained in 35% yield with 93% *ee* when $(DHQD)_2PHAL$ was used as the chiral Lewis base catalyst (Scheme 8).

In 2017, Huang and coworkers reported a regiodivergent [4 + 2] cycloaddition of α,β-unsaturated ketimines with 2,3-butadienoates, affording a series of hydropyridine derivatives in moderate to good yields under mild conditions [32–34]. The authors found that when DABCO was used as a Lewis base catalyst, then the α and β sites of allenoates participated in the formation of chemical bonds, while the β and γ sites of allenoates participated in the formation of chemical bonds in the presence of DMAP. Interestingly, absolute regioselectivity could be realized by only applying different nucleophilic tertiary amine catalysts (Scheme 9).

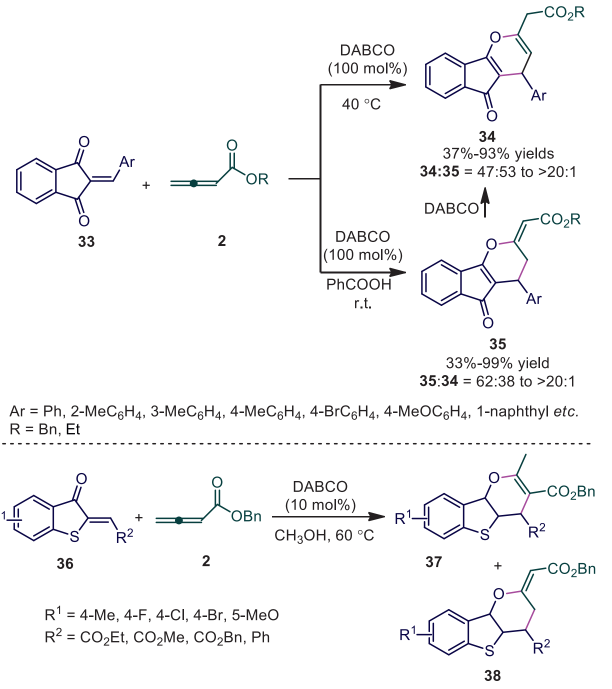
Our group is devoted to developing a novel Lewis base-catalyzed cycloaddition strategy [35–37]. In 2018, we reported a



Scheme 8. Divergence in the reactivity between amine- and phosphine-catalyzed cycloaddition reactions of allenoate with enynals.



Scheme 9. Divergent synthesis of hydropyridine derivatives *via* nitrogen-containing Lewis base mediated regioselective [4 + 2] cyclizations.



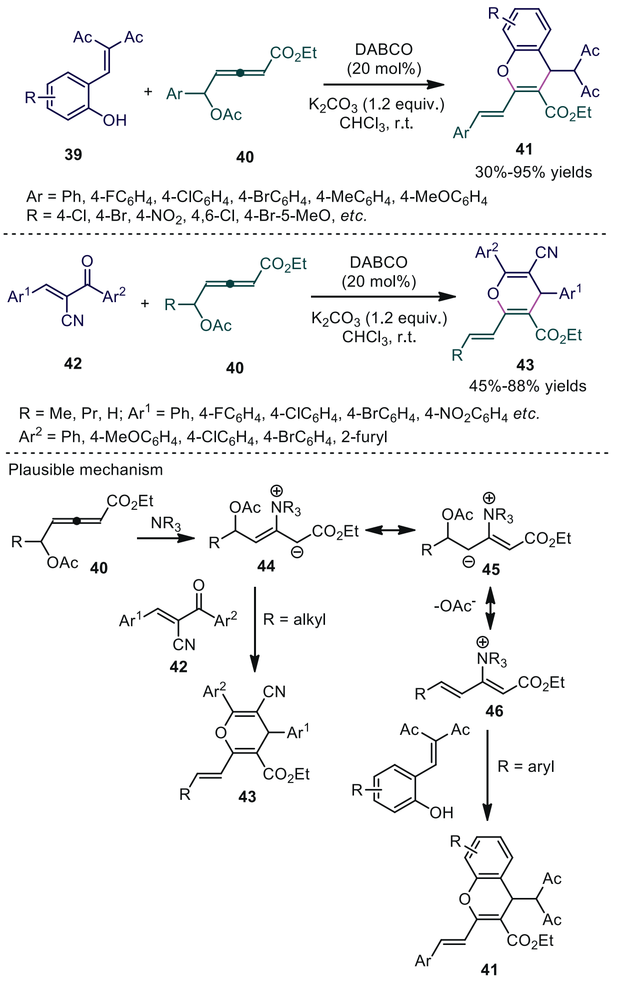
Scheme 10. DABCO-promoted [4 + 2] cycloaddition reaction of allenoates with 2-arylidene-1*H*-indene-1,3(2*H*)-diones.

DABCO-promoted [4 + 2] cycloaddition reaction of allenoates with 2-arylidene-1*H*-indene-1,3(2*H*)-diones, selectively giving annulated 4*H*-pyran **35** and annulated 3,4-dihydro-2*H*-pyran **34** in moderate to good yields, respectively [38]. Further study suggested that the catalyst (DABCO) played a dual role in involving a Lewis base-promoted [4 + 2] cycloaddition and the subsequent Brønsted base-mediated double bond isomerization. The role of the Brønsted base could be quenched selectively in the presence of a Brønsted acid ($PhCO_2H$), and the desired annulated 3,4-dihydro-2*H*-pyran **35** was thus obtained as major product. Later, Meng and coworkers developed a DABCO-catalyzed [4 + 2] annulation reaction between 2-alkylidenebenzothiophene-3(2*H*)-ones and allenoates, providing a series of functionalized benzothiophene-fused γ-pyran derivatives in moderate yields and selectivity (Scheme 10) [39].

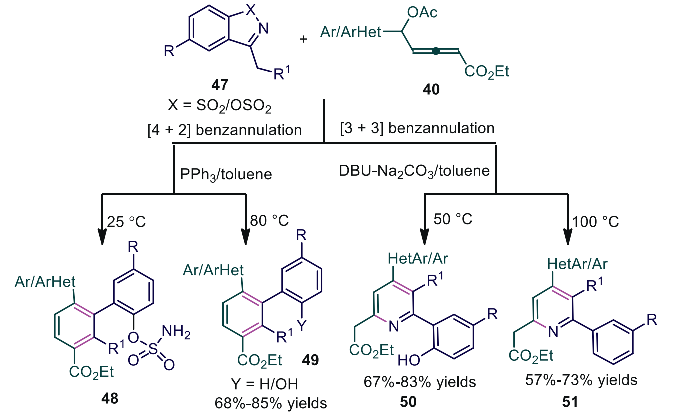
In early research, γ-substituted allenoates were thought to have low reactivity and selectivity and were not considered to be effective reactive substrates [40,41]. In 2009, Huang and coworkers described novel phosphine-catalyzed [2 + 4] cycloadditions of γ-methyl allenoate in which γ-CH_3 of the allenoates underwent cycloaddition to form chroman derivatives for the first time [42]. Thus, γ-substituted allenoates have received considerable interest from synthetic chemists and continued with studies of γ-substituted allenoates as synthons in cycloaddition reactions. In 2015, Tong and coworkers reported two different types of [4 + 2] cycloadditions of δ-acetoxy allenoates in the presence of DABCO [43]. The experiment suggested that the chemical behavior of allenoates under a DABCO catalyst was substrate dependent. Allenoates with an aromatic group at δ_C preferentially reacted with salicylaldehydes, delivering the desired 4*H*-chromenes **41**, while 4*H*-pyrans **43** could be obtained using allenoates with an alkyl group at δ_C and oxo dienes as reactive substrates. Mechanistically, the authors gave one reasonable explanation; for the case of δ-aryl allenoates under tertiary amine catalysis, the reactivity of zwitterionic intermediate **45** might be reduced owing to steric hindrance. Thus, intermediate **45** might undergo 1,2-elimination of the acetoxy group, giving electrophilic intermediate **46**. When δ-methyl-substituted allenoates were applied in this reaction, intermediate **45** might be unfavorable to formation *via* the interaction of allenoates with DABCO due to the lack of a conjugation effect imposed by the aryl substituent. In this event, zwitterionic intermediate **44** would be dominant, which furnished a different [4 + 2] annulation with a suitable electrophile under tertiary amine catalysis (Scheme 11).

In 2020, Swamy and coworkers developed Lewis base-mediated [3 + 3] or [4 + 2] benzannulation reactions of δ-acetoxy allenoates **40** with cyclic *N*-sulfonyl imines **47**, giving teraryl motifs **48**/**49** or 2-pyridinyl acetates (α-pyridyl acetates) **50**/**51** by simply switching the Lewis bases [44]. The authors found that changes in catalysts and temperature could result in the synthesis of different products. Under PPh_3 catalysis, the [4 + 2] benzannulation process gave functionalized teraryls by sequential Mannich coupling/C-N bond cleavage with retention or cleavage of the sulfamoyloxy group depending on the reaction temperature, while using DBU as the catalyst and Na_2CO_3 as the additive, the [3 + 3] annulation involving sulfonyl elimination *via* O–S or C–S bond cleavage occurred, affording 2-pyridinyl acetates in good yields (Scheme 12).

More recently, Swamy and coworkers reported catalyst-dependent chemo-, regio-, and stereo-selective [4 + 2] cycloadditions involving δ-acetoxy allenoate as a C4 synthon [45]. The experiment showed that the nucleophilic distinction between DABCO and DMAP resulted in significant differences in reactivity and selectivity. When using DABCO as the catalyst, Na_2CO_3 as the Brønsted base and AcOH as the Brønsted acid, the reaction occurred smoothly in toluene at 110 °C, affording desired adducts **52** in 55%–73% yields with absolute chemoselectivities. Benzannulation occurred in the presence of DMAP, giving unsymmetrical *m*-teraryl scaffold **53** in high yield (78%). The mechanistic study re-



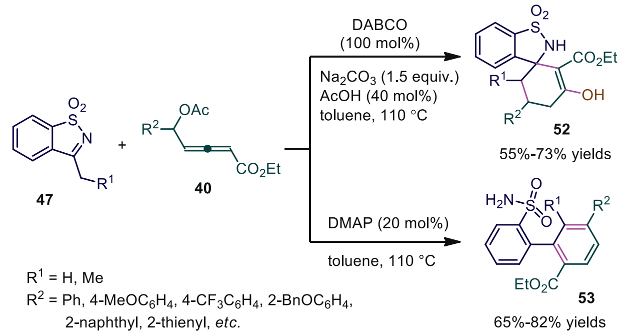
Scheme 11. DABCO-catalyzed divergent [4 + 2] annulations of δ-acetoxy allenoates with salicylaldehydes or oxo dienes.



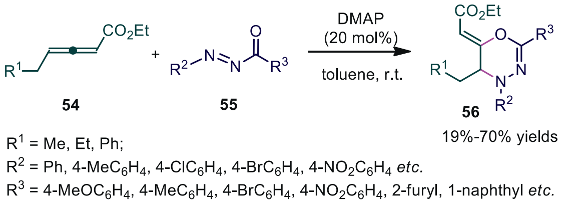
Scheme 12. Lewis base-switched [3 + 3] and [4 + 2] benzannulation reactions of δ-acetoxy allenoates with cyclic N-sulfonyl imines.

vealed that spirocyclic **52** and m-teraryl **53** motifs were formed in entirely different pathways at later stages, and DABCO-mediated spiro-annulation occurred *via* enol acetate–imine coupling. DMAP-catalyzed benzannulation proceeded *via* intramolecular Mannich coupling, proton transfers, and C–N bond cleavage (Scheme 13).

N-Acyldiazenes are an important class of diazenes with distinctive reactivity and are commonly used in NHC-catalyzed cycloadditions with ketenes and aldehydes [46,47]. In 2015, Meng and Wang reported an efficient DMAP-catalyzed [4 + 2] cycloaddition of allenoates and *N*-acyldiazenes, generating 1,3,4-oxadiazine derivatives in moderate to good yields [48]. The experiment showed that the nucleophilicity of catalysts played a key role in the reactivity, and other amines (such as DABCO, Et_3N, DBU) and phosphines (*e.g.*, PPh_3, PBu_3) shut down the cycloaddition completely (Scheme 14).



Scheme 13. Tertiary amine dependent chemo-, regio-, and stereoselective [4 + 2] annulations involving δ-acetoxy allenoate with cyclic *N*-sulfonyl imines.



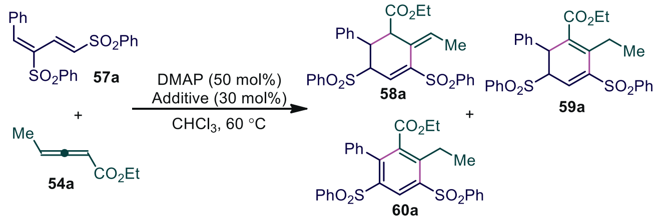
Scheme 14. DMAP-catalyzed [2 + 4] cycloaddition of allenoates and *N*-acyldiazenes.

In 2016, Huang and coworkers reported DMAP-catalyzed [4 + 2] benzannulations involving γ-substituted allenoates **54** and 1,3-bis(sulfonyl)butadienes **57** [49]. The experiment suggested that only DMAP was used as the catalyst, and multisubstituted cyclohexene **58a** and cyclohexadiene derivative **59a** were produced in moderate yields. Some additives, including organic bases (*e.g.*, NEt_3, DIPEA), inorganic bases (*e.g.*, CH_3CO_2Na, NaOH, Cs_2CO_3), and Brønsted acid (PhCOOH), could tune the selectivity of the reaction to give polysubstituted arene **60a**. It was noted that polysubstituted benzenes **60** with long alkyl chains, such as isobutyl or *n*-pentyl, could also be obtained in good yields without undergoing rearrangement (Scheme 15).

In 2019, Miao and coworkers disclosed a tertiary amine-catalyzed regiodivergent [4 + 2] cycloaddition of allene ketones or α-methyl allene ketones with benzylidenepyrazolones, constructing the corresponding tetrahydropyrano [2,3-*c*] pyrazoles in moderate to good yields [50]. Further study showed that formal α- and γ-[4 + 2] cycloadditions were found when quinine and DMAP were used as catalysts, respectively. The authors thought that the relatively electron-poor nucleophile quinine might stabilize carbon anion **24**, leading to the thermodynamically favored α-addition, while the relatively electron-rich nucleophile DMAP led to kinetically favored γ-addition (Scheme 16). Later, Zhong and coworkers also realized [4 + 2] cycloaddition involving benzylidenepyrazolone with ethyl 4-phenylbuta-2,3-dienoate under DBU catalysis [51].

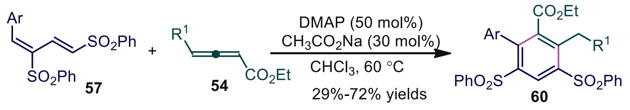
3. Tertiary amine-catalyzed [2 + 2] cycloaddition of allenoates with electrophiles

Azetidines are present as a partial structure of numerous natural products, biologically active compounds and pharmaceuticals. Thus, the development of effective methods for the assembly of functionalized azetidines from readily available starting materials is still of interest. In 2003, Shi and workers re-



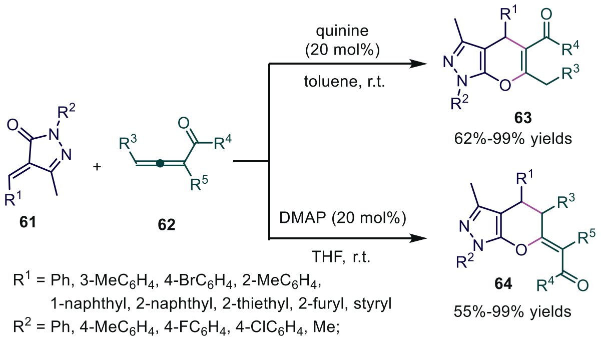
Entry	Additive (mol%)	Time (h)	Yield (%)		
			58a	**59a**	**60a**
1	no additive	24	52	18	-
2	Cs_2CO_3 (50)	54	-	-	48
3	NaOH (50)	48	-	-	38
4	$PhCO_2Na$ (50)	48	-	-	59
5	Et_3N (50)	34	-	-	59
6	DIPEA (50)	24	-	-	60
7	CH_3CO_2Na (50)	24	-	-	61
8	CH_3CO_2Na (30)	24	-	-	62
9	$PhCO_2H$ (30)	23	-	-	42

Substrate scope



Ar = 4-BrC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-ClC_6H_4, 2-MeC_6H_4, 1-naphthyl, thienyl *etc.*
R^1 = Me, ^{n}Bu, ^{i}Pr, Bn

Scheme 15. DMAP-catalyzed [4 + 2] benzannulation of γ-substituted allenoates and 1,3-bis(sulfonyl)butadienes.

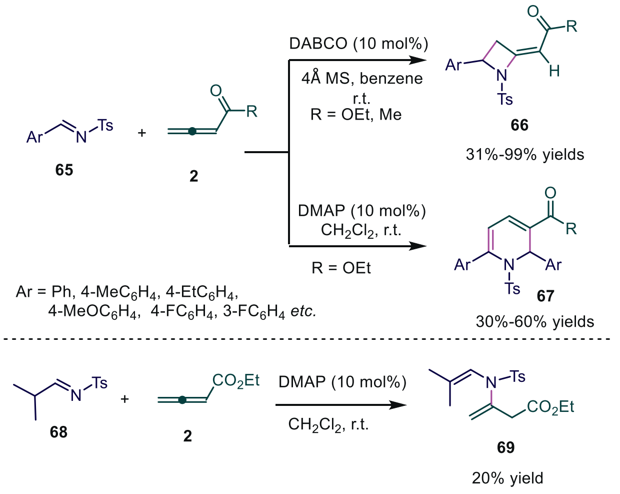


R^1 = Ph, 3-MeC_6H_4, 4-BrC_6H_4, 2-MeC_6H_4,
1-naphthyl, 2-naphthyl, 2-thiethyl, 2-furyl, styryl
R^2 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, Me;
R^3 = Ph, H, 4-FC_6H_4
R^4 = Me, Ph, 4-ClC_6H_4;
R^5 = H, Me

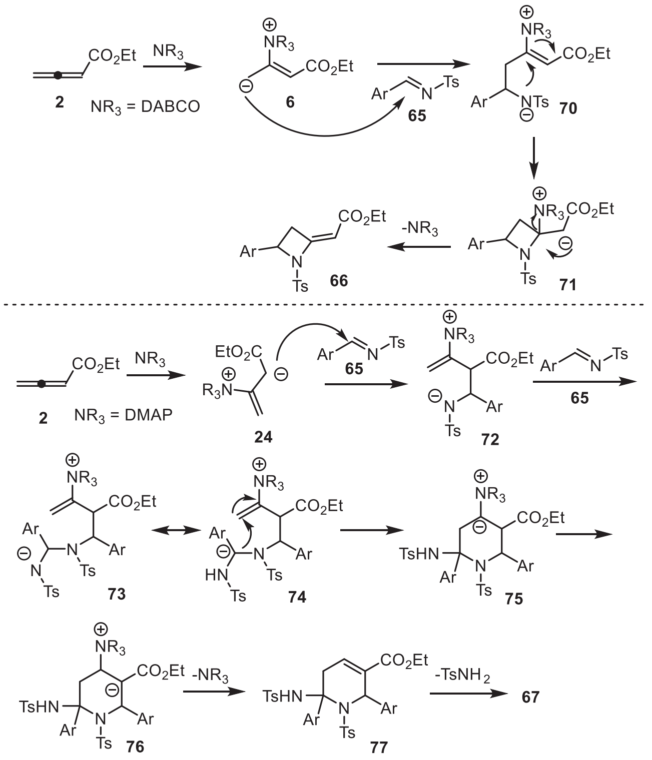
Scheme 16. Tertiary amine-catalyzed regiodivergent [4 + 2] cycloaddition of allene ketones or α-methyl allene ketones with benzylidenepyrazolones.

ported a tertiary amine-catalyzed cycloaddition reaction of ethyl 2,3-butadienoate or penta-3,4-dien-2-one with *N*-tosylated imines [52]. Screening the Lewis bases, the authors found that [2 + 2] cycloaddition adducts were obtained in the presence of DABCO. When DMAP was used as a Lewis base catalyst, the reaction occurred smoothly by “abnormal” [3 + 2 + 1] cycloaddition, affording the desired products in 30%–60% yields. Interestingly, when a relatively stable aliphatic *N*-tosylated imine was applied under DMAP catalysis, the reaction still proceeded smoothly, giving the corresponding 3-[(2-methylpropenyl)(toluene-4-sulfonyl)-amino]-but-3-enoic acid ethyl ester **69** in a 20% yield (Scheme 17).

The authors proposed a reasonable mechanism, as shown in Scheme 18. First, DABCO and DMAP acted as nucleophilic triggers and gave zwitterionic intermediate (allylic carbanion) **6**, which existed with resonance-stabilized intermediate **24** (enolate). When DABCO was used as a Lewis base catalyst, allylic carbanion **6** attacked the *N*-tosylated imine to produce intermediate **70**, which underwent intramolecular cyclization to give intermediate **71**. The final elimination of NR_3 from **71** afforded producted **66** and regenerated DABCO. Under DMAP catalysis, intermediate **24** was favorable, attacking an *N*-tosylated imine to give intermediate **72**, which attacked another *N*-tosylated imine to give intermediate **73**. Subsequent proton shift/intramolecular Michael addition gave intermediate **75**. Finally, another proton shift/NHT elimination furnished product **67** and regenerated DMAP (Scheme 18).

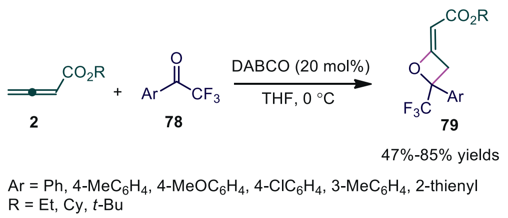


Scheme 17. Tertiary amine-catalyzed cycloaddition reaction of ethyl 2,3-butadienoate or penta-3,4-dien-2-one with *N*-tosylated imines.

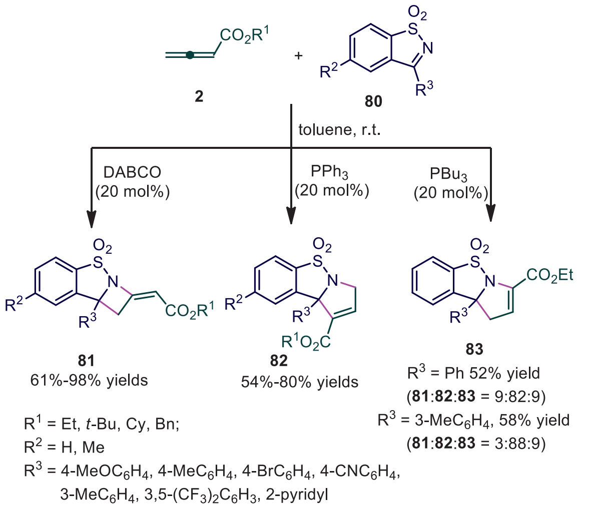


Scheme 18. Proposed mechanism for tertiary amine-catalyzed cycloaddition of allenoates with *N*-tosylated imines.

In 2011, Ye and coworkers discovered the DABCO-catalyzed [2 + 2] cycloaddition of allenoates and trifluoromethylketones, producing the corresponding 2-alkyleneoxetanes **79** in good yields with good diastereoselectivities [53]. It was noted that only [2 + 2] cycloaddition adducts were obtained in the presence of either DABCO or DMAP compared to that in Shi’s report (Scheme 19) [52]. In 2013, Selig and coworkers used bicyclic guanidine 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as a tertiary amine Lewis base



Scheme 19. DABCO-catalyzed [2 + 2] cycloaddition of allenoates and trifluoromethylketones.



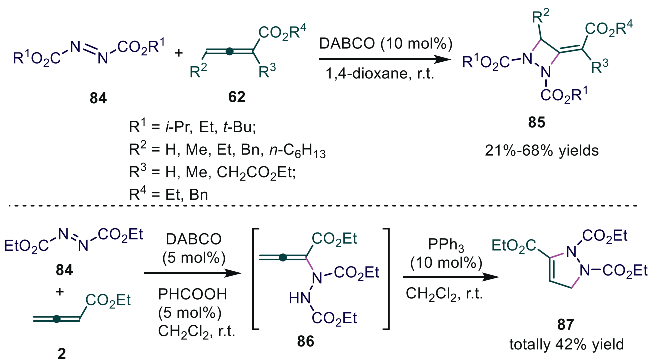
Scheme 20. Catalysts-controlled [2 + 2] or [3 + 2] cycloaddition of cyclic sulfonamides with allenoates.

catalyst, also finishing the [2 + 2] cycloaddition of allenoates with trifluoromethylketones [54].

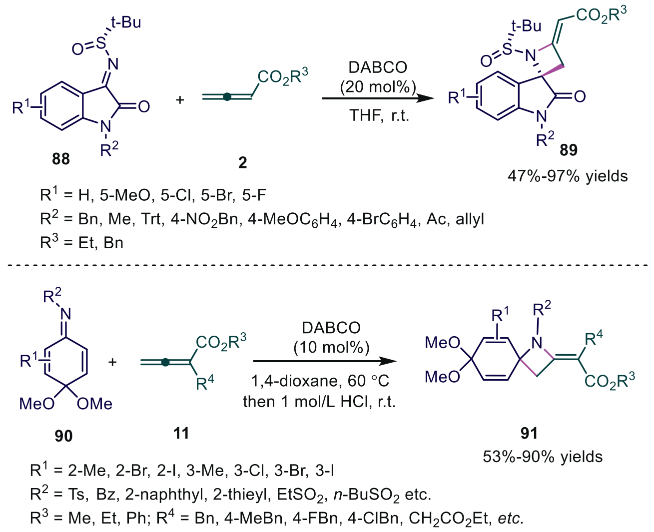
Cyclic ketimines or their derivatives have important applications in organic synthesis and medicinal chemistry because of their biological activity [55,56]. In 2012, Ye and coworkers reported a catalyst-controlled [2 + 2] or α-[3 + 2] cycloaddition of cyclic sulfonamides with allenoates, giving the corresponding sultam-fused azetidines and dihydropyrroles in good yields with high regioselectivities [57]. Interestingly, [2 + 2] cycloadducts **81** and [3 + 2] cycloadduct **82** were formed exclusively when DABCO and PPh_3 were applied as the catalysts, respectively. The reaction catalyzed by PBu_3 gave γ-[3 + 2] cycloadduct **83** predominately with litter cycloadducts **81** and **82** (Scheme 20).

In 2015, Xu and coworkers used azodicarboxylates as reactive substrates, finishing the DABCO-catalyzed [2 + 2] cycloaddition of allenoates [58]. In this report, the authors realized formal [3 + 2] annulation of allenoates and azodicarboxylates for the formation of pyrazoline by a DABCO/PPh_3 relay catalytic strategy (Scheme 21).

In 2016, Silvani and coworkers used chiral *tert*-butanesulfinyl ketimines as electrophiles and achieved DABCO-catalyzed [2 + 2] cycloaddition of allenoates, producing enantiopure spirooxindole-fused 4-methyleneazetidines in moderate to good yields [59]. Further study showed that α-substituted allenoates proved to be completely uncreative under the reaction conditions, and the authors thought that the result could be ascribed both to the stereoelectronic influence of the methyl group on the allenoate and to the high steric challenge inherent in the formation of the tetrasubstituted double bond joined to the spiroazetidine ring. More recently, Huang and Cheng described the DABCO-catalyzed [2 + 2] cycloaddition of quinone imine ketals with allenoates (Scheme 22) [60].



Scheme 21. DABCO-catalyzed [2 + 2] annulation of allenoates with azodicarboxylates.

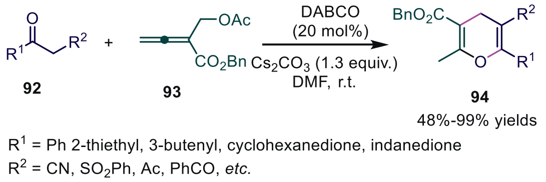


Scheme 22. DABCO-catalyzed [2 + 2] cycloaddition of allenoates with *tert*-butanesulfinyl ketimines or quinone imine ketals.

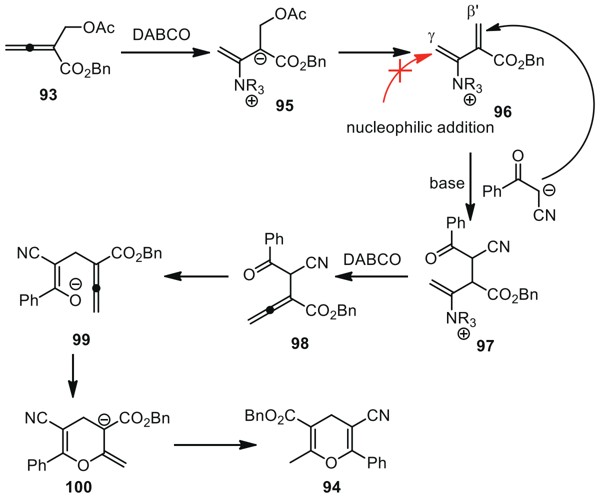
4. Tertiary amine-catalyzed [3 + 3] cycloaddition of allenoates with electrophiles

In 2003, Kwon and coworkers developed a novel strategy using α-substituted allenoates as substrates to first achieve phosphine-catalyzed [4 + 2] cycloaddition [61]. Inspired by this result, Tong and coworkers used β'-acetoxy allenoates as substrates and successfully applied them to phosphine-catalyzed [4 + 1] annulations with 3-oxo-3-phenylpropanenitrile. Based on this, the novel DABCO-catalyzed [3 + 3] cycloaddition of β'-acetoxy allenoates with 3-oxo-3-phenylpropanenitrile was developed, producing the corresponding 4-substituted 4*H*-pyrans **94** in 48%–99% yields [62]. In a preliminary attempt, asymmetric [4 + 2] annulation was examined with quinine catalysts, affording **94a** in 82% yield and 19% *ee*. The authors thought that this DABCO-catalyzed [3 + 3] annulation probably proceeded through a mechanism involving the destruction and subsequent reconstruction of the stereogenic center of the β'-carbon (Scheme 23).

A plausible mechanism was proposed by the authors. As shown in Scheme 24, attack by DABCO to the β-carbon of the allenoate initiated the addition–elimination process to yield intermediate **96**. According to previous reports, it was unlikely that Michael-type addition of **93** to the γ-position of intermediate **96** was due to the poorer ability of the ammonium ion to stabilize the ylide. Apparently, intermediate **97** was generated by a Michael-type addition of **93** to the β'-position of **96** with the help of a base. Next, 1,2-



Scheme 23. DABCO-catalyzed [3 + 3] cycloaddition of β'-acetoxy allenoates with 3-oxo-3-phenylpropanenitrile.



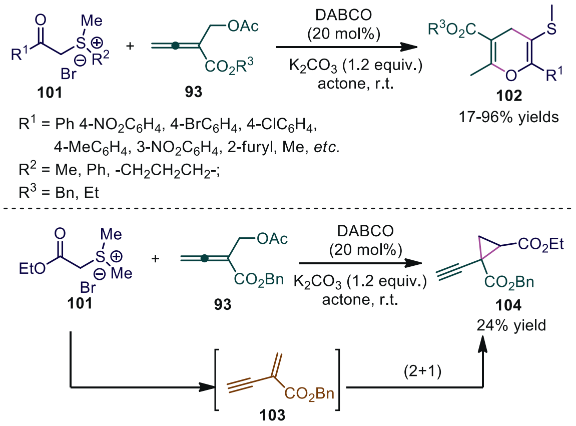
Scheme 24. Plausible mechanism for DABCO-catalyzed [3 + 3] cycloaddition of β'-acetoxy allenoates with 3-oxo-3-phenylpropanenitrile.

elimination of DABCO delivered intermediate **98**, which was followed by 6-*endo-trig* type oxo-Michael addition to form intermediate **100**. Finally, compound **94** could be obtained by continuous isomerization and protonation. It was noted that intermediate **98** could be isolated when the reaction of **92** and **93** was conducted in benzene solvent for a short period of time, and the conversion of **98** to **94** was achieved with a longer reaction time (Scheme 24).

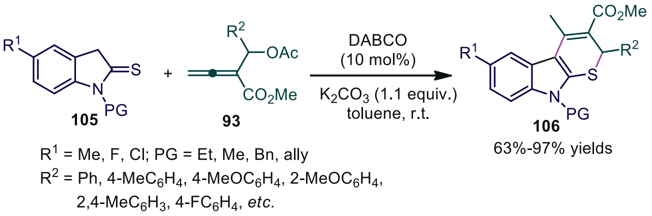
Sulfur ylides show unique and important reactivity in organic synthesis [63,64]. Over the past decade, chemical transformations involving sulfur ylides have attracted much research interest, with a number of novel sulfur ylide-based reactions with high synthetic potentials having emerged for the synthesis of epoxide, aziridine and cyclopropane. In 2012, Tong and coworkers reported a DABCO-catalyzed [3 + 3] annulation between β'-acetoxy allenoates and sulfur ylides, and they synthesized S-containing 4*H*-pyran **102** in good yields [65]. Further study showed that only a 17% yield of **102j** was obtained using methyl ketone-stabilized sulfonium salt as the nucleophile even with a prolonged reaction time. In addition, cyclopropane derivative **104** was obtained in 24% yield when ester-stabilized sulfur ylides were used under the same conditions. According to Lee's report [66], the authors thought that the stability of key intermediate **103** played a critical role in the result (Scheme 25).

Later, the authors also achieved DABCO-catalyzed formal [3 + 3] annulations of β'-acetoxy allenoates with indoline-2-thiones, providing the desired thiopyrano[2,3-*b*]indoles **106** in 63%–97% yields (Scheme 26) [67].

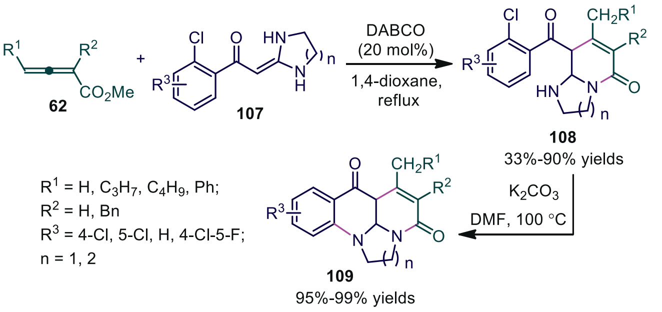
In 2011, Li and Wen reported a DABCO-catalyzed [3 + 3] cycloaddition of 2-(2-chloroaroyl)methyleneimidazolidines with allenoates, affording functionalized imidazo(pyrido)[1,2-*a*]pyridines **108** in moderate to good yields [68]. Further study revealed that the corresponding imidazo(pyrido)[3,2,1-*ij*][1,8]naphthyridines **109** were obtained in the presence of K_2CO_3 (1.0 equiv.) in DMF at 100 °C for approximately 6 h in almost quantitative yields of 95%–99%. The experimental results suggested that this domino process involved nine reactive sites. One C-C bond, two C-N bonds, and two new rings are constructed with all reactants efficiently utilized in the chemical transformation (Scheme 27).



Scheme 25. DABCO-catalyzed [3 + 3] annulation between β'-acetoxy allenoates and sulfur ylides.



Scheme 26. DABCO-catalyzed formal [3 + 3] annulations of β'-acetoxy allenoates with indoline-2-thiones.

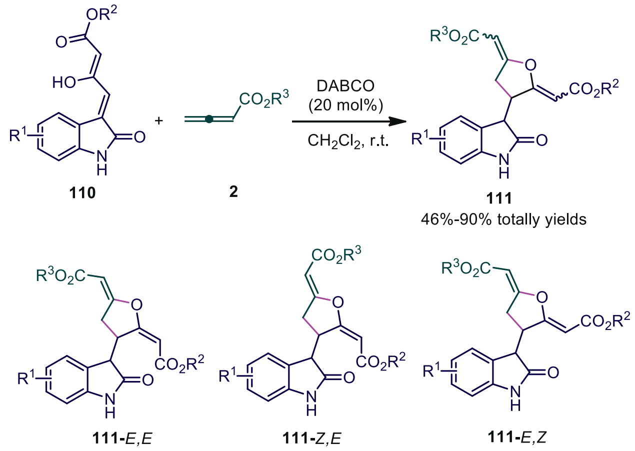


Scheme 27. DABCO-catalyzed [3 + 3] cycloaddition of 2-(2-chloroaroyl) methyleneimidazolidines with allenoates.

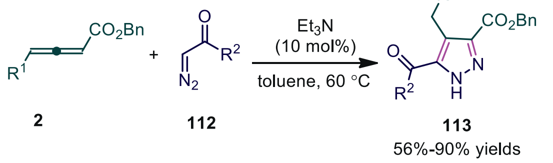
5. Other tertiary amine-catalyzed cycloadditions of allenoates with electrophiles

In 2014, Meng and coworkers reported the DABCO-catalyzed [3 + 2] cycloaddition reaction between 3-oxo-4-(2-oxoindolin-3-ylidene) butanoates and allenoates, furnishing 2,3,5-substituted tetrahydrofurans in high yield [69]. In this report, moderate chemoselectivity was obtained in most cases, and three isomers were simultaneously synthesized in which two of them could be isolated. Interestingly, isatins without *N*-protecting groups were used to successfully finish the cycloaddition in the reaction, which was highly desirable for practical synthetic applications (Scheme 28).

More recently, Ma and coworkers reported the Et_3N-catalyzed [3 + 2] cycloaddition reaction of allenoates with diazoesters, dia-

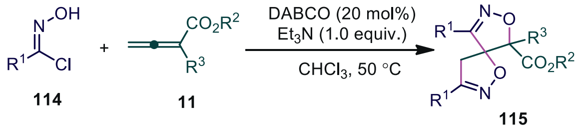


Scheme 28. DABCO catalyzed the [3 + 2] cycloaddition reaction between 3-oxo-4-(2-oxoindolin-3-ylidene)butanoates and allenoates.



R^1 = H, Me, Bn, $ClCH_2CH_2$, EtO_2CCH_2, Ph, 2-thiethyl
R^2 = BnO, CH_2=$CHCH_2O$, Ph, NEt_2, N(OMe)Me

Scheme 29. Et_3N-catalyzed [3 + 2] cycloaddition reaction of allenoates with diazo compounds.

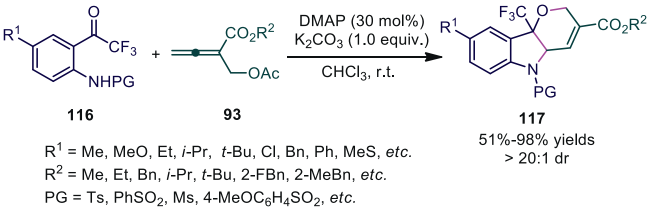


R^1 = Ph, $4\text{-}FC_6H_4$, $4\text{-}BrC_6H_4$, $4\text{-}MeOC_6H_4$, $3\text{-}FC_6H_4$, $3\text{-}MeC_6H_4$, $2\text{-}BrC_6H_4$, 2-naphthyl
R^2 = Me, Et, t-Bu; R^3 = $4\text{-}ClC_6H_4$, $4\text{-}BrC_6H_4$, $4\text{-}MeC_6H_4$, $3\text{-}BrC_6H_4$, $3\text{-}ClC_6H_4$, *etc.*

Scheme 30. DABCO-catalyzed double [3 + 2]-cycloadditions between nitrile oxides and allenoates.

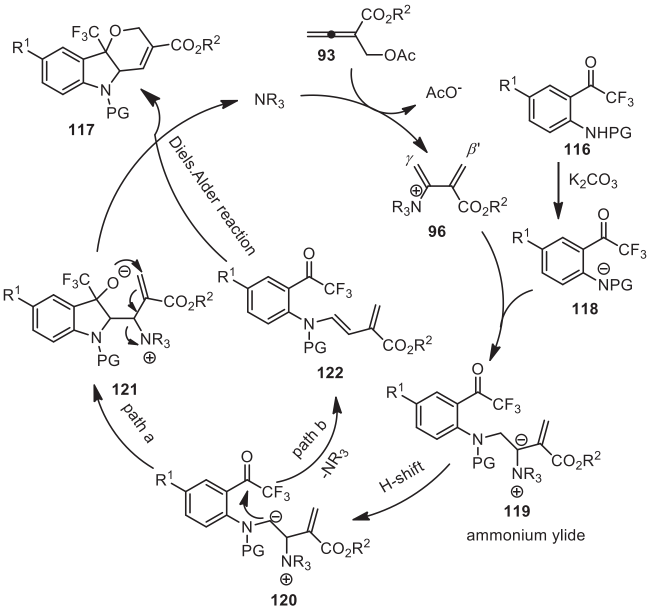
zoketones, and diazoamides, leading to a group of pyrazoles in 56–90% yields (Scheme 29) [70].

Allenoates have proven to function as 1,2-, 1,3-, and 1,4-dipole synthons when reacting with a variety of electrophilic partners in the presence of tertiary amines. Only two chemical bonds are generated in most reactions. Because of the multiple reactive sites in allenoates, it was possible that more sites took part in the formation of chemical bonds at the same time [71]. In 2018, Li and coworkers discovered double [3 + 2] cycloadditions between nitrile oxides and allenoates in the presence of DABCO with Et_3N in which DABCO was used as a nucleophilic Lewis base catalyst with Et_3N as the Brønsted base [72]. The α, β, γ sites of allenoates took part in the formation of chemical bonds in the reaction. It was noted that nitrile oxides with aliphatic substituents were not suitable substrates in this reaction (Scheme 30).



R^1 = Me, MeO, Et, i-Pr, t-Bu, Cl, Bn, Ph, MeS, *etc.*
R^2 = Me, Et, Bn, i-Pr, t-Bu, 2-FBn, 2-MeBn, *etc.*
PG = Ts, $PhSO_2$, Ms, $4\text{-}MeOC_6H_4SO_2$, *etc.*

Scheme 31. DMAP-catalyzed [4 + 1]/[3 + 3] domino sequential cycloaddition reaction between *o*-aminotrifluoroacetophenones and β'-acetoxy allenoates.

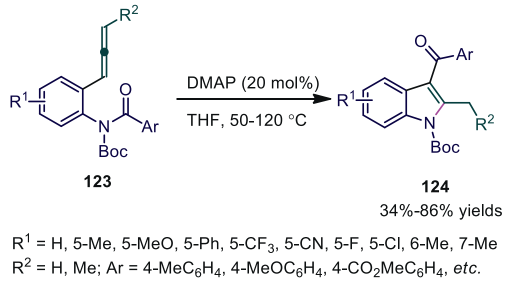


Scheme 32. A plausible reaction pathway of DMAP-catalyzed [4 + 1]/[3 + 3] domino sequential annulation of allenoates.

In 2020, Huang and coworkers reported the DMAP-catalyzed [4 + 1]/[3 + 3] domino sequential cycloaddition reaction between *o*-aminotrifluoroacetophenones and β'-acetoxy allenoates, which afforded a series of CF_3-containing tetrahydropyrano[3,2-*b*]indole products in high to excellent yields with a single diastereoselectivity [73]. In previous reports, all nucleophiles were added to the β'-position of intermediate **96** because no empty orbital in the ammonium ion of intermediate **96** stabilized the carbanion in the subsequently generated ammonium ylide. To overcome these limitations, the authors used DMAP with a π-conjugated system as the catalyst, and the p-π conjugation between the carbanion and the aromatic ring of DMAP could stabilize the corresponding ammonium ylide. Thus, Huang first realized the addition of nucleophiles to the γ position of intermediate **96** (Scheme 31).

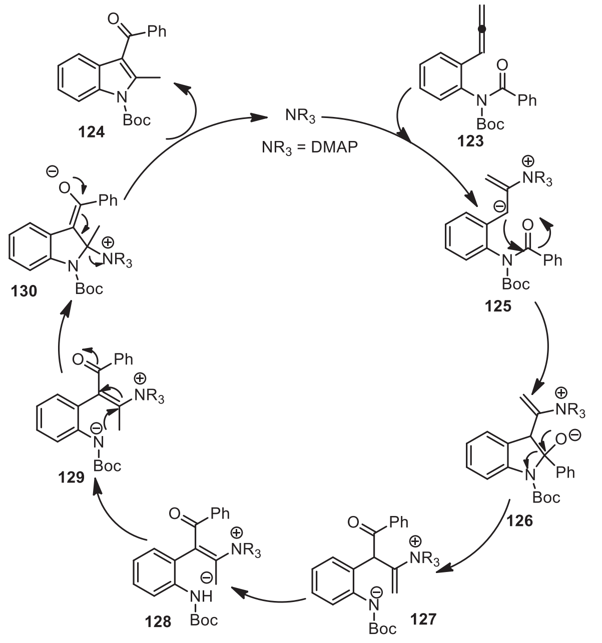
The author proposed a plausible reaction pathway, as showed in Scheme 32. Nucleophilic addition of DMAP to allenoates was followed by 1,2-elimination of acetate to generate intermediate **96**. Subsequently, γ-addition of intermediate **118** to intermediate **96** formed intermediate **119**. Next, tandem proton shift (**120**) /intramolecular 1,2-addition/intramolecular S_N2' substitution in intermediate **121** yielded product **117** with DMAP catalyst regeneration. The authors thought that it was also possible for it to undergo tandem 1,2-elimination *via* the DMAP/intramolecular Diels–Alder reaction, affording product **117** directly (Scheme 32).

Lewis base-catalyzed cycloaddition of electron-deficient activated allenes has been broadly investigated. However, due to the high activation barrier, the Lewis base-catalyzed cycloaddition reaction of nonactivated or weakly activated allenes has rarely been reported. In 2020, Xia and Yu developed the DMAP-catalyzed amino-acylation of arylallenes, providing 2-methyl-3-aroylindole products in good yields [74]. Compared with traditional amine moieties as waste after C(O)–N bond cleavage, both acyl and amine moieties are incorporated into the products *via* selective cleavage of amide C–N bonds in the reaction. The experimental results suggested that the Boc group was essential for successful C–N bond cleavage, and no C–N bond cleavage was detected in the absence



R^1 = H, 5-Me, 5-MeO, 5-Ph, 5-CF$_3$, 5-CN, 5-F, 5-Cl, 6-Me, 7-Me
R^2 = H, Me; Ar = 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-CO$_2$MeC$_6$H$_4$, *etc.*

Scheme 33. DMAP-catalyzed amino-acylation of arylallenes.



Scheme 34. A plausible reaction pathway of DMAP-catalyzed amino-acylation of arylallenes.

of N-Boc protection. Further mechanistic studies showed that the amino acylation of allenes occurred in an intramolecular fashion, successive [1,4]- and [1,6]-proton transfers occurred in the recycling system, and a nitrogen anion intermediate assisted the proton transfer processes *via* protonation/deprotonation (Scheme 33).

According to control experiments and DFT calculations, the authors proposed a plausible reaction pathway. The nucleophilic addition of DMAP to aryl allene **123** first occurred, affording zwitterionic intermediate **125**, which then underwent nucleophilic addition to the amide's carbonyl to give intermediate **126**. Subsequently, successive C-N bond cleavage (**127**)/[1,4]-(**128**)/[1,6]-proton transfer (**129**)/nucleophilic addition of a nitrogen anion to the β-position of the α,β-unsaturated ketone resulted in intermediate **130**. Finally, expulsion of DMAP produced product **124** (Scheme 34).

6. Conclusions

Tertiary amine catalysis has emerged as a prominent and reliable strategy for constructing functionalized mono-, multi- and spiro-cyclic structures that have important applications in the fields of natural products synthesis and pharmaceutical design. In the presence of tertiary amines, allenoates can be applied as C2, C3 and C4 synthons to participate in many kinds of cycloaddition reactions, such as [4 + 2], [2 + 2], [3 + 2], [3 + 3], or sequential annulation reactions. In this review, we have summarized the latest progress of tertiary amine-catalyzed annulation reactions involving diverse allenoates. We hope that this updated review provides our readers with a systematic overview of this research field so that recent advances in tertiary amines catalytic annulation reactions can be better appreciated and recognized. More importantly, we hope that tertiary amine catalysis will continue to evolve and provide even more powerful and versatile synthetic methods to advance the state-of-the-art of ring construction strategies, broadening the horizons of organocatalysis. Thus it is reasonable to believe that new advances in tertiary amine-promoted cycloaddition involving allenoates will come.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgments

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